Acta Paediatrica

Vol. 42 · November 1953 · No 6

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Almqvist & Wiksells Boktryckeri AB UPPSALA

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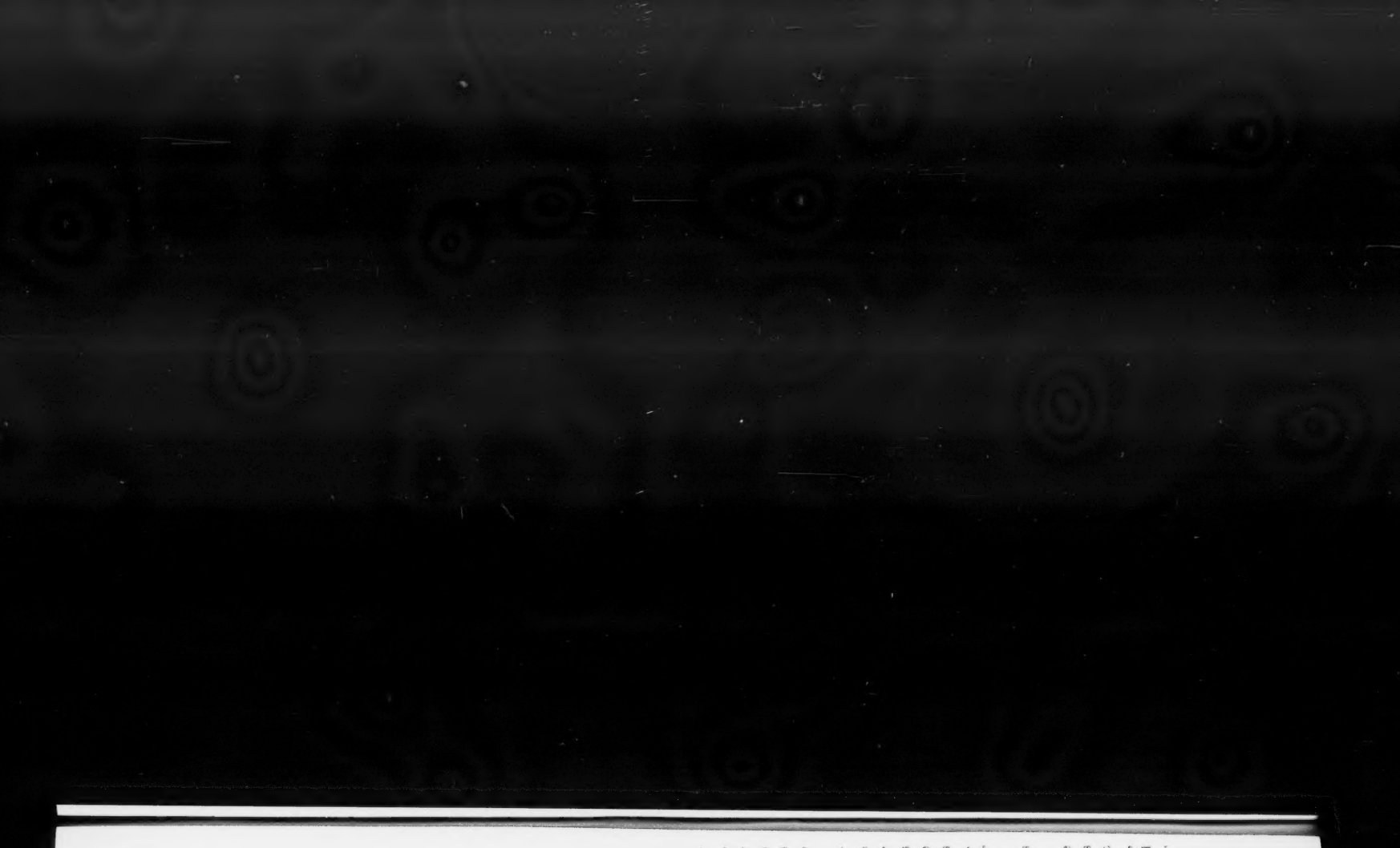

Acta Pædiatrica **42**: 491—498. Nov. 1953

From the Department of Pediatrics
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Ill-Health among School Children who had Previously Attended Day Nurseries

by LENNART HESSELVIK

It has long been known that the care of children in daynurseries is often accompanied by a high sickness rate, and this has been dealt with exhaustively by many authors. The immediate effects of this on the general health of the children has been investigated from various points of view. A survey of the relevant literature is found in a monograph by the author dealing with the occurrence of respiratory infections in children at daynurseries (HESSELVIK).

A problem quite separate from this is the following question: to what extent is the later health of children, especially during the first few years at school, affected by day nursery infections? The acute specific infections of childhood constitute a group by themselves. For obvious reasons, children in day nurseries contract diseases like measles, whooping cough and so on in the pre-school age to a greater extent than children who spend their time at home. It follows that such diseases are more frequent during the first school years among children belonging to the latter category.

The remaining group consists of the "non-specific" causes of ill-health, of which the catarrhal infections of the respiratory tract and their sequelae comprise by far the greatest part. The frequent infections during the day nursery years may affect subsequent health in many different ways: immunity can develop, or increased susceptibility may follow. Results of earlier investigations in this field have largely been conflicting. Among investigations carried out on children, the Medical Research Council's analysis of infections among children at English boarding schools is particularly interesting. Here, no correlation could be found between the incidence of colds during two observation periods made at an interval of three years. The present author was unable to find any difference in the incidence of colds between new children at a day nursery and those who had been attending for one year.

It seemed advisable to study the importance of earlier infections by reinvestigating, after a lapse of four years, the author's previous series of day

nursery children and those cared for at home. During the earlier period of survey, 1946—47, these two series showed a difference in incidence of respiratory infections: there were twice as many days of fever and more than twice as many days with nasal discharge among the day nursery children compared with the others; otitis was three times mere common in the former group.

The two primary schools serving the district where the previous investigations were made were chosen for the present investigation. In one school the lowest four forms, and in the other the fourth form only were included, owing to the age distribution of the children in the previous series. All children in these forms took part, even those who had not been included in the previous series.

The investigation consists of an analysis of ill-health during term time. For children in the former school this covers a period of 1, 3, 5, or 7 terms. In the latter it covers 8 terms, as the investigation here took place six months later. (The Swedish school year consists of two terms.)

The school data consist of information partly from the medical cards kept for all children, and partly from the form registers which record the children's day to day presence or absence from school, with reasons for absence.

Information regarding attendance at day nurseries in the pre-school years was obtained through a questionnaire. In addition, questions were included regarding attendance at nursery schools, because the previous investigation had also shown somewhat more ill-health among nursery school children in comparison with "home" children.

The medical cards of the schools contained notes on epidemic diseases with the dates of occurrence, major accidents, and illnesses of long duration, but no data on trivial ailments. Usually no note of the diagnosis is made in the form register (when a child is ill). In a great many cases it was therefore necessary to question the mothers. This was done in all cases where the child had had an epidemic disease during term, and in all cases of absence for more than two weeks, where the information could not be obtained elsewhere. The above particulars of attendance at pre-school institutions, and sickness, were obtained for all children in the forms in question (see above). Children who left for, or came from, other schools during the investigation period were not included in the final review of the series, for a preliminary survey seemed to show considerable variations in ill-health from year to year. If these children had been included, any deviation from the average susceptibility to infection which they showed would have caused a distortion of the results.

The scope of the series is given in the following table:

	No. of terms					Total	Boys	Girls
	1	3	5	7	8			
Former "day nursery children"* . .	21	23	13	9	16	82	33	49
Former "nursery school children"**	41	38	16	26	20	141	64	77
Former "home children"	74	56	54	56	47	287	149	138
	136	117	83	91	83	510	246	264

* average stay at day nursery more than 2 years (26.8 months).

** average stay at nursery school *c.* 1½ years (18.3 months).

Results

Specific infectious diseases.

In this series measles was by far the most common infectious disease during pre-school and school years. The incidence of measles in the day nursery group compared with the "home" group is shown in Fig. 1.

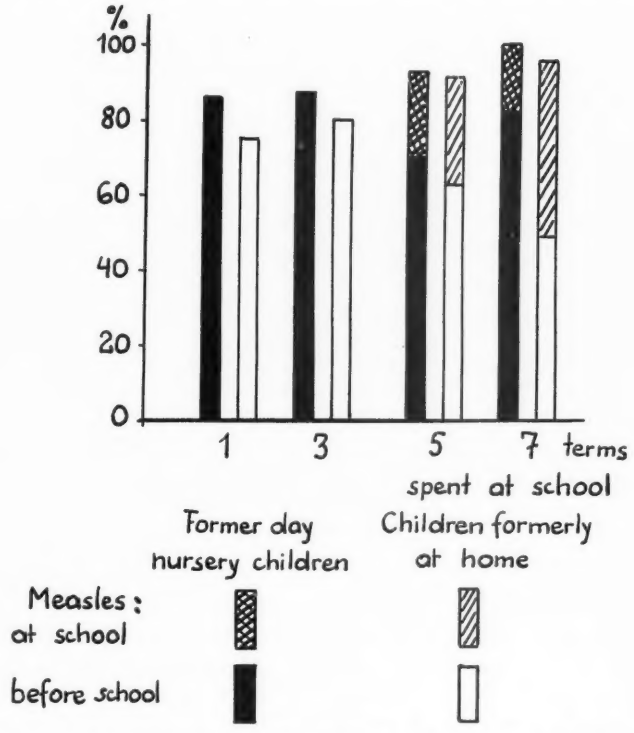

Fig. 1. Incidence of measles in school children previously cared for in day nurseries and own homes, respectively.

Thus, taking all groups together it could be seen that many more of the former day nursery children had had measles before starting school than had the former "home children." The difference is statistically significant ($0.01 < p < 0.02$). In the two groups where measles had occurred during the years at school the former "home children" showed a higher frequency than those who had been at day nurseries, which was to be expected under the circumstances.

Non-specific diseases.

Calculations on the remaining causes of ill-health (the non-specific diseases) are based on the number of days of absence from school for reasons of sickness in relation to the possible number of attendances, after allowance has been made for absence due to specific infections and to surgical conditions, including accidents. Although a more detailed analysis of the non-specific diseases cannot be given it can be assumed that they correspond closely to the catarrhal respiratory infections and their sequelae.

The distribution of the non-specific diseases within the groups of children covered by the investigation is given in the following table and is illustrated graphically in Fig. 2.

Absence due to non-specific diseases (days of absence in per cent of possible attendance days):

	No. of terms				
	1	3	5	7	8
Former "day nursery children" . .	5.16	3.92	6.65	5.19	6.66
Former "nursery school children" .	5.68	4.80	4.65	4.80	4.78
Former "home children"	7.01	4.54	5.17	4.93	6.18
Mean	6.33	4.50	5.30	4.81	5.93

The differences between the groups as shown in the table are relatively small and do not show any tendency to a greater susceptibility to disease among any of the groups. A statistical analysis of the values obtained for former "day nursery children" and former "home children" has nevertheless been carried out for the 7 and 8 term children, covering the 7 terms common to both. As was expected, the trifling difference was not significant (former "day nursery children" 5.69 %, former "home children" 5.41 %).

It should be pointed out that ill-health in all the groups covering children between 7 and 10–11 years proved to be more or less constant, corresponding to 5 % absence. In other words, no definite correlation with age was apparent.

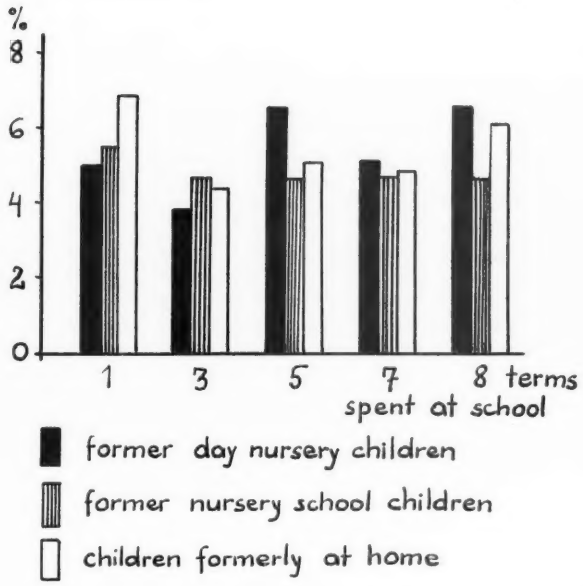

Fig. 2. Absence from school due to non-specific diseases (days of absence in per cent of possible attendance days).

No consistent tendency to greater ill-health among boys or girls could be found.

Further analysis of the type of sickness seemed to be justified because definite differences between the various categories might manifest themselves only during the earliest period at school. Ill-health during each term is given in Fig. 3.

Certain variations in the incidence of sickness seemed to occur throughout. A high incidence of ill-health in one calendar year seemed to be followed by a year of comparatively low incidence, and vice versa. Otherwise, the curves for the various groups show a striking similarity. No consistently higher incidence of ill-health could be found in any of the forms within any of the groups at any time during the period of observation.

In analogy with this, an analysis of individual absenteeism was carried out. The results were compared with figures obtained in a previous investigation on the same children for catarrhal infections of the respiratory tract (incidence of pyrexia and nasal discharge). No definite correlation seemed to exist between these values which were obtained following an interval of 4 years.

The above result does not justify the conclusion that the higher incidence

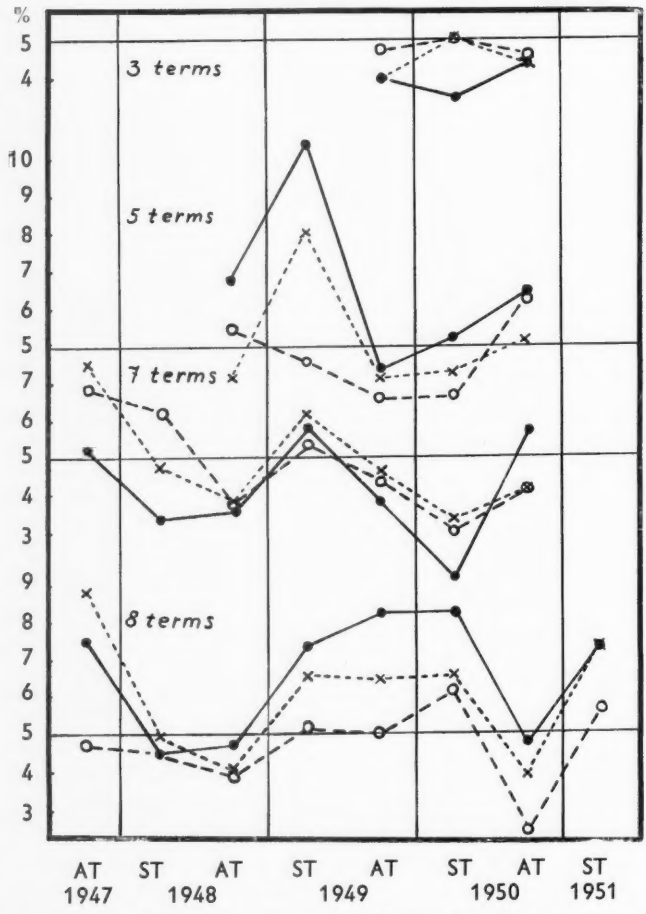

Fig. 3. Absence from school due to non-specific diseases for each term (days of absence in per cent of possible attendance days).

AT = autumn term. ST = spring term. ●———● former day nursery children.
○— — —○ former nursery school children. ×— — —× children formerly at home.

of catarrhal infections of the respiratory tract characteristic of day nursery children—and to a certain extent of nursery school children—in comparison with children tended exclusively at home, has no effect whatsoever upon subsequent health during the school years. An exceptionally large series would be necessary to support such a contention. It can, however, be assumed that, among the factors governing ill-health due to non-specific causes in children during the first years at school, previous day nursery and nursery school care plays a minor role.

Summary

An investigation has been carried out in order to examine whether the frequent infections occurring in children cared for at day nurseries had any significant effect on subsequent ill-health during the early school years. The study was made on a series of children who had been the subject of an investigation four years earlier. It had been found previously that a substantially higher sickness rate prevailed among children in day nurseries, and also to a certain extent among nursery school children, than among those cared for exclusively at home.

Among the common specific infections of childhood it has now been found, as expected, that measles occurred more frequently among the children formerly at home than among the former day nursery children, the latter having already had the disease before starting school. Non-specific diseases (chiefly respiratory infections and their sequelae) were found to occur to more or less the same extent in all the three groups. Attendance at these types of institutions must therefore be assumed to have no great influence on the later occurrence of these conditions.

Among the children investigated, ill-health due to non-specific causes was found to occur at about the same level in all groups, corresponding to about 5 % absence.

No definite correlation could be established between ill-health recorded four years earlier and the frequency of absenteeism of the same individuals reported during the period of the present investigation.

Morbidité parmi les écoliers qui ont été antérieurement placés dans des garderies de jour.

Une étude fut faite dans le but de découvrir si les infections fréquentes présentées par les enfants qui ont été placés dans les garderies pendant la journée ont une influence ultérieure sur ceux-ci durant les premières années scolaires. Il s'agit d'enfants qui ont été déjà l'objet d'études à ce point de vue pendant les 4 dernières années. L'auteur a pu mettre en évidence que par rapport aux enfants élevés exclusivement à la maison, ceux qui se trouvaient dans les garderies de jour, ceux qui en étaient issus, et ceux qui fréquentent les écoles maternelles montraient un pourcentage plus élevé de morbidité. Une exception est à signaler cependant parmi les maladies infectieuses en ce qui concerne la rougeole. Cette dernière maladie est plus fréquente chez ceux qui sont restés antérieurement à la maison que chez les enfants issus des nurseries, ces derniers ayant eu déjà la maladie avant l'âge scolaire. Rien de spécial en ce qui concerne les autres infections spécifiques. Les infections non spécifiques (principalement respiratoires et leurs séquelles) ne montrent pas de prédominence nette, dans les 3 groupes. Les stages dans ces institutions n'ont donc pas d'influence sur la santé ultérieure des enfants. Parmi les enfants étudiés, la fréquence de la morbidité par infection non spécifique était à peu près la même dans les différents groupes. Elle entraînait environ 5 % d'absences. Il est impossible d'établir une corrélation définitive entre la morbidité d'il y a 4 ans et la fréquence de l'absentéisme des mêmes individus actuellement.

Gesundheitsverhältnisse bei Schulkindern, welche vorher Tagesheime besuchten.

Eine Untersuchung wurde durchgeführt, um festzustellen, ob die häufigen Infektionen bei Kindern in Tagesheimen irgendeinen Einfluß auf die Gesundheitsverhältnisse während des ersten Schuljahres haben. Dazu ausgesucht wurde eine Reihe von Kindern, die in der Hauptsache identisch war mit einer Gruppe, welche 4 Jahre vorher Gegenstand einer Untersuchung war. Eine weit höhere Erkrankungsrate liegt bei Kindern in Tagesheimen und in gewissem Umfang auch bei Pflege-

schulkindern im Vergleich zu solchen, die nur zu Hause aufgezogen werden, vor. Bei den gewöhnlichen spezifischen Infektionen des Kindesalters wurden, wie erwartet, Masern häufiger bei Kindern gefunden, welche von zu Hause kamen, als unter ehemaligen Tagesheimkindern, weil letztere diese Infektion schon vor der Schulzeit durchmachten. Nichtspezifische Erkrankungen (hauptsächlich Luftwegsinfektionen und deren Folgen) fanden sich in mehr oder minder gleichem Ausmaß bei allen 3 Gruppen. Das Vorhandensein derartiger Institutionen dürfte deshalb keinen großen Einfluß auf das spätere Auftreten solcher Erscheinungen haben. Unter den untersuchten Kindern schienen die Gesundheitsverhältnisse bei unspezifischen Ursachen in allen Gruppen auf etwa gleicher Höhe, entsprechend einer Abwesenheit von ungefähr 5 %, zu liegen. Endgültige Beziehungen zwischen den vor vier Jahren verzeichneten Gesundheitsverhältnissen und der während der jetzigen Untersuchung festgestellten Häufigkeit der Abwesenheit bei den gleichen Individuen konnten nicht aufgestellt werden.

Salud en niños de edad escolar los cuales habían asistido previamente a guarderías de lactantes.

Se ha realizado una investigación con el ánimo de descubrir cual ha sido la frecuencia de las infecciones ocurridas en niños que habían asistido a las guarderías y si ello condicionaba un efecto sobre la subsiguiente salud–enfermedad durante los primeros años escolares. Se hizo en series de niños idénticas con otro grupo el cual había sido objeto de una investigación similar 4 años antes. Se encontró entonces que un tiempo de indisposición substancialmente elevado prevalecía entre los niños que asistían a las guarderías y que se extendía también en los parvularios escolares en relación con los que permanecían en casa. Entre las infecciones comunes de la infancia se ha hallado como era de esperar que el sarampión ocurre mas frecuentemente entre los niños que anteriormente han permanecido en su casa que entre los que han estado en guarderías de lactantes ya que éstos últimos han pasado la enfermedad antes de asistir a la escuela. Las enfermedades no específicas, especialmente afecciones respiratorias y sus secuelas, parecen tener la misma extensión en los 3 grupos. Los cuidados en estos tipos de instituciones no parecen tener una gran influencia en la frecuencia posterior de estas afecciones. Entre los niños investigados la relación salud–enfermedad debida a causas no específicas fué hallada sobre el mismo nivel en todos los grupos correspondiendo sobre ausencias de 5 %. No se puede establecer una correlación definida entre los datos de salud–enfermedad recogidos 4 años antes y la frecuencia o ausencia en los mismos individuos establecida durante el período de la presente investigación.

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Received 20.8. 1952.

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Acta Pædiatrica **42**: 499—505. Nov. 1953

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On the Etiology of Dysostosis Mandibulo-Facialis

by HELGE GRANRUD

The realization that exogenic injury to the mother during the first three months of pregnancy can produce embryonic malformations—embryopathies—has given rise to eager research to discover the causes of the different types of malformations. It is recognized that a very important factor is the stage of embryonic development reached at the time of the injury. That group of cells which is in the most lively state of development—organizers—is the most vulnerable, which accounts for the very limited damage the embryo may sustain. These cells are of high differentiation and cannot be replaced, and the damage is, therefore, irrevocable. The organ involved is permanently affected. Through experiments on animals STOCKARD has shown that different injuries which occur at identically the same stage of embryonic development can result in the same defect, whereas identical injuries occurring at different stages can result in different defects. Furthermore, MORRISON has shown by animal experiments that exogenic chemical and physical influence can result in exactly the same changes as those of genetic origin—phenocopies.

We wish to discuss here a type of facial deformity—dysostosis mandibulo-facialis—and an atypical form of the same.

In literature we find reference to the anomaly as far back as 1889, but it was first described in detail by FRANCESCHETTI in 1944 and 1949, when the term dysostosis mandibulo-facialis was introduced.

It is assumed that these anomalies are caused by a retarded growth in the ontogenetic development of the mesoderm in the mandibular arch and its surroundings, the hyomandibular cleft. The time when the damage occurs should be about the seventh week of embryonic development (5th to 10th week). The etiology is obscure. Earlier it was assumed to be genetic, and an irregular dominant heredity was shown. DEBUSMAN described a family with 9 cases in three generations and stressed that it looked as if the anomaly was inherited through females. This does not, however, hold true. If one looks more closely at the genealogy of these cases, one will find that besides dysostosis mandibulo-facialis a number of other defects and abnormalities are also present, and in addition there is a decidedly increased frequency of menstrual disturbances, abortions and neomortality. This also tallies with LANDTMAN's investigations on mothers with abnormal children, among whom he detected

an increased frequency of earlier abortions, ante-partum haemorrhage, and other disorders during pregnancy such as acute infections. From this it can perhaps be inferred that dysostosis mandibulo-facialis may also be caused by pathological conditions of the uterus, either in the form of dysfunction or, as seems to be the case in one of the patients to be mentioned here, a transient mechanical injury to the uterus.

Information about possible exogenic injury is either scanty or non-existent in reports published so far. WOLFF has, however, produced dysostosis mandibulo-facialis-like conditions in chicken embryo by means of roentgen rays, and WARKANY produced similar conditions in rats by putting them on a diet lacking in riboflavin. FRASER and FAINSTAT are probably correct in maintaining that the cause of congenital malformations can be of three types, (i) genetic, (ii) environmental damage to the embryo, or (iii) the combined result of heredity and environmental damage.

Six cases of these anomalies have been admitted to the Pediatric Department of the Oslo University Hospital in recent years. In one of the cases no anamnestic information is available, and it has not been possible to obtain proper information since. In the remaining five cases all the mothers had had some disorder or other during the first three months of pregnancy, which cannot be excluded as a possible cause of the abnormality. It could not be traced to heredity except in one case, where a cousin of the patient had a deformity of the ear. It is felt, therefore, that it may be of interest to give an account of the five cases about which we have anamnestic information. They comprise three cases of dysostosis mandibulo-facialis—two of which are of the so-called complete type and one of the incomplete type—and also two of the atypical form.

Case No. 1.—Steinar, born 1939, admitted 1945. Dysostosis mandibulo-facialis, complete type. No deformities in the family. Mother had influenza when she was approximately one month pregnant, accompanied by haemorrhage lasting for three to four days. As the mother died of pulmonary tuberculosis shortly before the child was admitted, more detailed information cannot be obtained. The patient is an only child. — Examination on admission revealed: Antimongolian slanting eyes with coloboma of the outer part of the lower palpebra on both sides. Hypoplasia of facial bones, particularly the zygomatic bone, but also of the maxilla and mandible. Deformed ear cartilage on both sides, the helix thickened and curled up. Left external auditory canal very narrow, the right one normal. Normal ear drums. Reduced hearing. Nasal cavities narrow. Position of teeth irregular. Pronounced caries. Late in losing milk teeth. No fistulas or cleft formations. Otherwise normal conditions and normal mental development.

Case No. 2.—Mona, born 1946. Admitted 1946. Died 1950. Complete type of dysostosis mandibulo-facialis (Fig. 1). No deformities in the family. Mother had rubella during 12th week of pregnancy. The patient is the first of two children, the youngest was born in 1951, normal. Examination on admission: Antimongolian slanting eyes with coloboma of the outer part of the lower palpebra on both sides. Hypoplasia of facial bones, in particular zygomatic bone, and also of mandible and maxilla. Maldeveloped ear cartilage on both sides, completely deformed and partly

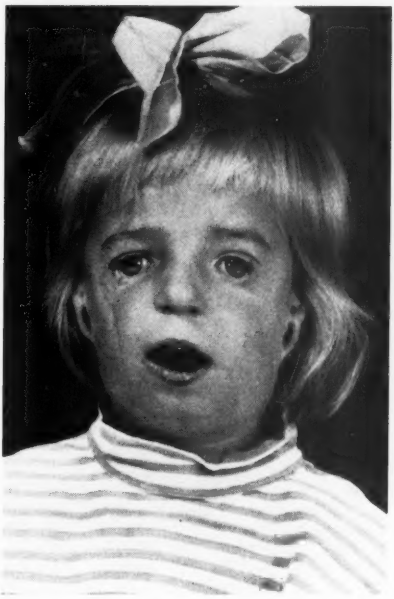

Fig. 1. Case No. 2. Complete type of dysostosis mandibulo-facialis.

joined to the facial skin. No external auditory canals, reduced hearing. No fistulas or cleft formations. The case record on later admission in 1949 states: Mental development not particularly retarded. — X-ray revealed rudimentary maxilla and mandible with narrow sinuses, zygomatic arch little developed, lower orbital margin interrupted. The organs of the inner ear were present. Towards the end the patient had repeated attacks of dyspnoea, twice accompanied by convulsions. She died during the last attack.

Case No. 3.—Tormod, born 1946, admitted 1952. Incomplete type of dysostosis mandibulo-facialis (Fig. 2). No deformities in the family, some cases of asthma. Mother admitted to hospital during the fifth week of pregnancy for diphtheria. The patient is the eldest of two children, the younger being normal. Admitted for asthma. Examination on admission: Slight antimongolian slanting eyes. Minor coloboma of lower palpebra on left side. Slight hypoplasia of the facial bones on both sides. Right ear situated rather low. Thick ear cartilages, normal auditory canals. Hearing normal. No fistulas or cleft formations. Normal mental development. X-ray: no defects of the facial bones.

Case No. 4.—Aase, born 1942. Admitted 1947. Atypical form (Fig. 3). No deformities in the family. In the beginning of the second month of pregnancy a doctor attempted to provoke abortion by injecting an iodine solution into the uterine cavity followed by manual compression of the uterus. Slight haemorrhage for three to four weeks. As this stopped, quinine was given a fortnight later without the desired

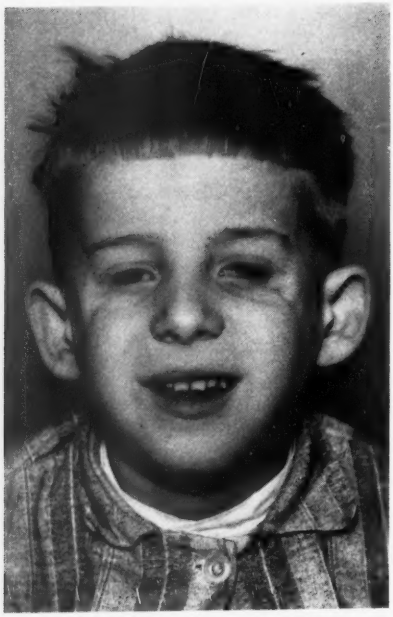

Fig. 2. Case No. 3. Incomplete type of dysostosis mandibulo-facialis.

effect. She felt "heavy" during pregnancy, but she went full term and the birth was normal. The patient is the third of four children, the others are normal. The patient was backward in developing, could not sit by herself before she was two or walk unaided before three. Mentally retarded. — Examination on admission: Of gracile build, height 103 cm (normal 110 cm), weight 14.5 kg (normal 16.5 kg), cranial circumference 45.5 cm (normal 50 cm). The palpebral fissure on the left side smaller than on the right, with small atrophic palpebrae. Sursumvergence of the eyeball so that the lower part of the cornea is bare, and in this area there is a lagophthalmic keratitis. Hypoplasia of the left half of the face and left-sided peripheral facial paralysis. The skin of the face bluish-red and thickened. Left ear cartilage completely deformed, consisting only of some folds of skin with traces of cartilage in some of them. The external auditory canal a cul-de-sac 1 cm deep, and mastoid process flattened. Hearing apparently normal. Protruding sternum. Precordial pulsation and strong systolic murmur of maximum intensity at the apex. No fistulas or cleft formations. Somewhat retarded mentally, I.Q. 62. X-ray: no air in the mastoid process and no external auditory canal on the left side. Facial bones: no defects. Heart: multiple malformations. Encephalography after air insufflation: normal.

Case No. 5.—Christine, born 1948, admitted 1948, died 1948. Atypical for m. A cousin of the patient has a slightly deformed ear, otherwise no deformities in the family. Mother had hydramnion—three litres of amniotic fluid at birth. Prolonged labour. Forceps delivery. No other children. — Examination on admission: Maldevel-

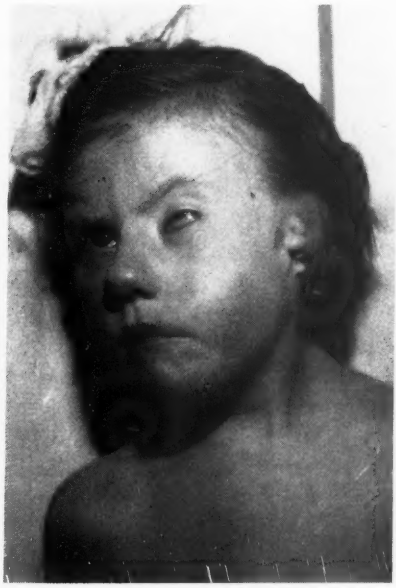

Fig. 3. Case No. 4. Atypical form of dysostosis mandibulo-facialis.

oped and multiple deformities. Length 43 cm, weight 2360 g. Cranial circumference 31 cm. Right eye: microphthalmia, cornea cloudy and turbid, shallow chamber. Coloboma of the iris below, as well as of the choroid. Possibly glaucoma. Left eye: normally sized eyeball, cornea clear, but coloboma of the iris and choroid. Hypoplasia of left side of the face. Left ear cartilage deformed, almost completely lacking, consisting only of a small curled-up flap of skin. The external auditory canal appears merely as a narrow slit. Congenital heart disease. Contracture deformity of the arms (arthrogryposis). Pes equino-varus with furrows on the toes. — X-ray: deformed upper limbs because of soft tissue contractures, bony structure normal. — Autopsy: Cerebrum, complete and total agyria. Heart, persistent foramen ovale and ductus arteriosus, haematoma of valves. Bicornute uterus. Oblong, soft ovaries.

Discussion

In the first three cases the following are the exogenic factors which must be considered as a possible cause of the anomaly: influenza with uterine haemorrhage in the fifth week of pregnancy, rubella in approximately the twelfth week, and diphtheria in approximately the fifth week. In the atypical cases hydramnion may have been the cause in one of them, and an attempted abortion in the fifth week of pregnancy in the other. Thus, there are two cases of virus infection plus one case where diphtherial toxins might have had an influence on the embryo. Of greatest interest is case no. 4,

where an attempt was made to interrupt the pregnancy during the critical period, and where no other reason for the deformity can be traced.

WEYERS is of the opinion that mechanical damage, such as an attempt at inducing an abortion by means of some "home remedy" during the critical period, may be the cause of such deformities, and has published one such case. WEYERS' case is, however, somewhat complicated, for there is a concurrent hydrocephalus, apparently because of toxoplasmosis. Even so, the case has much in common with that described above, and presents the following deformities, all located on the right side: open palpebral fissure with lagophthalmic keratitis, facial hypoplasia with paresis of the facial nerve, greatly deformed outer ear consisting only of a flap of skin, no external auditory canal, and in addition cleft palate.

The typical keratitis present in both these cases is a so-called keratitis neuroparalytica Marchesani. This is due to a hypofunction, which may well be the result of damage to the nerve as it passes through the retroauricular bone which, in these cases, is subjected to osteodystrophia. This has also been regarded as a possible cause of the unilateral facial hypoplasia. The frequent occurrence of hearing defects may also, perhaps, be attributed to the same cause.

One cannot, therefore, exclude exogenic factors as a cause of the deformities in the cases discussed here, factors which may in part have acted quite locally such as mechanical or toxic damage to the uterus or the embryo.

Summary

Five cases of dysostosis mandibulo-facialis are recorded. In all of them there are exogenic factors which may possibly account for the deformities. Particular attention has been paid to one case where an abortion was attempted during the fifth week of pregnancy.

Sur l'étiologie de la dysostose maxillofaciale

L'auteur rapporte 5 cas de dysostose maxillofaciale. Dans tous ces cas on relève des facteurs exogènes qui peuvent entrer en ligne de compte dans la génèse de cette déformité. L'attention est particulièrement attirée sur un cas chez lequel un avortement fut tenté pendant la cinquième semaine de la grossesse.

Über die Ätiologie der Dysostosis mandibulo-facialis.

Fünf Fälle von Dysostosis mandibulo-facialis werden beschrieben. In all diesen Fällen liegen exogene Faktoren vor, die für die Deformierungen möglicherweise verantwortlich gemacht werden können. Die Aufmerksamkeit wird hauptsächlich auf einen Fall gelenkt, bei dem ein Abtreibungsversuch in der 5. Schwangerschaftswoche unternommen worden war.

Sobre la etiología de la disostosis mandibulo-facial.

Se describen cinco casos de disostosis mandibulo-facial. En todos ellos se encuentran factores exógenos que podrían ser una posible causa de las deformidades. Se llama especialmente la atención sobre un caso en el que se intentó un aborto durante la quinta semana del embarazo.

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Received 23.10. 1952.

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Acta Pædiatrica **42**: 506—513. Nov. 1953

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Unilateral Skin Vessel Crises in the Newborn

by GILLIS HERLITZ

In the complicated pattern of clinical symptoms which may accompany the cerebral birth injuries in newborn infants the changes in skin colour often predominate. They are generally associated with disturbances in the frequency, rhythm and strength of the respiratory movements. Sometimes the skin colour may be markedly cyanotic (livid asphyxia) and sometimes markedly pale (pallid asphyxia). In either case there is a considerable oxygen deficiency in blood and tissues. The asphyxia is often associated with cerebral hemorrhage and frequently it is a symptom of the injury. Asphyxia may also occur in a newborn infant without any cerebral lesion being present.

Asphyxia is a state of suffocation, which represents a general deficiency of oxygen which may occur *in utero* or *during partus*, and is not necessarily a consequence of absent respiratory movements. The causes of the intrauterine asphyxia may vary (premature separation of the placenta, compression of the umbilical cord, etc.). The hypoxia causes a minor or major suppression of the irritability of the medullary respiratory centre, which is thought to be due to a form of exhaustion on account of excessive adequate irritation of the centre with excess of carbonic acid in the blood. This state of exhaustion may persist for short or long periods after delivery, leading to irregularity or absence of respiration. If the function of the respiration centre is initially defective, as in the case of premature infants, or if it is influenced by narcotics or other remedies applied to the mother, it persists longer before regular and effective respiratory movements are observed. During this period the asphyxia increases further, and the risks of its deleterious actions on the cerebrum increase correspondingly.

The two forms of cerebral lesions which may occur in association with delivery are: intracranial hemorrhages, and lesions of the ganglion cells after prolonged hypoxia. The mechanism of the intracranial hemorrhages is in dispute. The former theories of the mechanism, viz. compression on and tearing of the tentorium and certain vein during labour, are now rarely considered to account for the hemorrhages in more than a minority of cases

(RYDBERG) including those with the severest hemorrhages. The possibility of an asphyxic condition as being a direct cause of intracranial hemorrhages in the newborn is now accepted by an increasing number of authors. The asphyxia causes venous hyperemia and stasis, which, in the children with fragile vessels (as described here), may be thought to result in vasorupture. It then seems obvious that, if the asphyxia causing the stasis may produce such an increase of pressure in the brain vessels that it leads to a rupture of their walls, the general increase of pressure in the cerebrum which is a direct consequence of the violent compression during labour must also play a considerable part in the occurrence of hemorrhages. This, however, does not follow as a matter of course. Whilst the compression on the head is going on during labour, the pressure outside the vascular walls is almost equal to that inside, which is due to the fact that if the intracranial pressure exceeds the arterial blood pressure, the latter rises through irritation of the vasomotor centre to a level which moreover is above the compression pressure (Cushing's law). If, however, the compression pressure suddenly decreases — when the labour pains cease — it may be thought that the reflex mechanism does not function rapidly enough, and that the difference between the intra- and the extravascular pressure becomes sufficiently great to permit rupturing of the vascular walls. It therefore appears to be of vital importance to the fetus that the compression pressure decreases slowly and not abruptly. As far as I know, the mode of the decrease of the compression pressure has not been the object of detailed studies. If a stasis in the cerebral vessels occurs because of circulatory disturbance during asphyxia, it is possible that the irritability of the vasomotor centres decreases owing to the hypoxia, so that the intravascular pressure does not run parallel to the extravascular pressure in the usual manner. It is obvious then that the conditions for sudden differences in pressure and therefore for intracranial hemorrhages must increase.

It seems as if the difference between the intra- and extravascular pressure need not be very great before hemorrhages occur. This is, at least, true of the peripheral vessels. In a child suffering from whooping cough it may be seen how hemorrhages occur in the conjunctiva during the attack. If a baby is allowed to suck its own arm for a while, petechial hemorrhages will soon appear. I tried once to construct an apparatus to check umbilical bleedings in newborn infants after the cord-stump had fallen off; it consisted of a small round cell which was placed over the navel, and which was provided with a double rail at the border, by which the apparatus was fastened to the skin by suction and adhered there with a very insignificant negative pressure. The experiments failed because of the skin hemorrhages that soon appeared at the site of suction. I thought it was a partial phenomenon of the hemorrhagic diathesis, but the skin bleedings appeared just as easily in healthy infants.

Thus the mechanism of intracranial hemorrhages, no doubt, is of complex nature, although there are good reasons for accepting that the asphyxia may give rise to them alone. In cerebral hemorrhages in the newborn the general hemorrhagic tendency, which for other reasons is characteristic of the initial postnatal period, should also be taken into consideration.

If an intracranial hemorrhage has occurred — through asphyxia or otherwise — the respiratory centre is frequently affected by the hemorrhage thus leading to disturbances of the respiratory movements with hypoxia and alteration of skin colour. The asphyxia is then a consequence of the cerebral hemorrhage and not the reverse. In most instances it is impossible to find out which of them appears first, the asphyxia or the cerebral hemorrhage, and which of them is the cause of the other. If the infant is aphyxtic, and particular symptoms from the cerebrum are absent, it cannot be decided always whether or not a cerebral injury is present. In the case of the pallid asphyxia the probability of its presence is very great, but in cases of blue asphyxia, the problem must often be left open. KEHRER, however, is of the opinion that a fairly prolonged cyanotic condition in an infant in whom the respiratory tracts are free and who has no congenital heart disease is due nearly always to an intracranial hemorrhage. Several authors share this view, the importance of the hypoxemic lesions is emphasized in this connection. Very often brain injuries may give fairly tardy symptoms; in particular, this is said to apply to the small hemorrhages in the medulla (SEITZ). The hemorrhages in the brain-stem are nearly always microscopical (SCHWARTZ). Anatomical examinations of premature infants have revealed that microscopical hemorrhages in medulla and pons are equally common whether the child has had respiratory difficulties or not (HIRVENSALO). These observations have suggested that the small hemorrhages are not always of great importance. That capillary hemorrhages or small extravasations, observable with the aid of microscopy, are absent rarely in the brains of the newborn is also stated by RYDBERG. Evidently some of these bleedings may be a terminal phenomenon.

In this respect one should consider that several children who have been asphyxtic at birth incur microscopical changes in the medulla and other places, which never give rise to symptoms or, if they do, only symptoms of such a nature as to be easily overlooked. I have observed some infants who had been slightly asphyxtic at birth, without exhibiting other signs of cerebral injury at that time (with one exception), but who subsequently presented a very characteristic change of the skin colour which, as far as I know, has not been described before, and which I think must be associated with similar microscopical lesions in the medulla.

Case 1. A boy, born December 30th, 1945, at full term. The mother para II, healthy. Labour began on December 30th at 4 a.m. Discharge of amnion liquid at 5.30 a.m.

and delivery at 6.20 a.m. (dextro-occiput presentation), Birth weight 3 330 g. The amnion liquid slightly tinged. The child was cyanotic at birth and did not cry. Suction was immediately applied to the throat, and a little clear blood was removed. Subsequently short spells of breathing occurred at long intervals. After bathing the colour became natural and the respiratory movements followed in close succession. The infant was stimulated with tonocard and lobeline and was transferred to the Children's Hospital 90 minutes after birth. On examination slight cyanosis was still present round the mouth, the temperature was subnormal, and the child cried feebly. No signs of hemorrhage in the throat. The large fontanelle was not tense, nor were there any other signs of cerebral injury. Inner organs normal. Recovered quickly in the course of the day, the cyanosis faded and the cry became stronger.

During the subsequent days small twitchings of mouth and skin of the forehead were observed sometimes. On January 3rd the patient, who was lying on his right side, suddenly developed complete pallor of the left side of the body, including the head, with sharp delimitation in the median line, whereas the right half of the body was of normal colour. The change disappeared when the patient was turned over on his left side after a couple of minutes. He did not show anything abnormal, nor were any signs of cerebral injury observed. X-ray of heart and cervical region (cervical ribs, if any) disclosed normal conditions. The temperature was normal.

He was discharged well on January 7th. Twitchings or changes of the skin colour were not noted after January 3rd.

On June 13th, 1946, the boy was re-examined. He had been perfectly well all the time and had developed normally. Any symptoms suggesting brain lesion had not been observed. Nor were there any signs of the sequelae of cerebral injury.

Case 2. A boy, born November 9th, 1946, six weeks before full term. The mother para I, healthy. The child was born after 18 hours' labour by occiput delivery. Birth weight 1760 g. Was cyanotic at birth and did not cry. After repeated alternate baths he was immediately transferred to the Children's Hospital. The hands were then slightly cyanotic, whereas the skin of the body was pink. The temperature was subnormal. The respiration was normal. The large fontanelle was not tense, nor were there any other signs of cerebral lesions. Inner organs normal. The child was placed in an oxygen incubator and the condition soon improved.

On November 14th he suddenly developed considerable redness all over the right half of the body, with sharp linear delimitation in the median line. The left half of the body, which was rather pale, contrasted strongly with the right. Changing the child's position did not influence the condition which disappeared after a couple of minutes. Nothing abnormal was found. Nor were any signs of cerebral injury demonstrable.

On November 18th at noon the same phenomenon was observed on the same side and under otherwise similar conditions. The pupils were equal and reacted to light. In the morning the temperature had increased to 39.2° C without demonstrable cause, but it soon decreased to 37.0° C without any measures being taken. In the afternoon the temperature was found to be reduced to 35.7° C, but immediately afterwards returned to normal. During the two preceding days the temperature had been subnormal, and without apparent cause a peak to 38.4° C was again noted on November 21st; otherwise the temperature was normal all the time. There were considerable vomitings and frequent stools during the first two weeks after birth, but otherwise he did not present any deviations from the normal course in a premature infant.

On December 20th he was discharged in good condition without presenting any signs of cerebral lesions or further changes of temperature or skin colour.

The patient was re-examined on January 26th, 1951. He had been healthy and developed normally. Defects of cerebral or other nature were not demonstrable.

Case 3. A boy, born September 29th, 1947, two months before full term. The mother para II, healthy. The infant was born by breech presentation. Birth weight 2140 g. Cyanotic at birth, was immediately transferred to the Children's Hospital. Presented there rather severe universal cyanosis and irregular respirations, and the skin was slightly oedematous. Temperature subnormal. The large fontanelle was not tense, nor were any other signs of cerebral injury observable. Inner organs normal. The condition improved after oxygen therapy in an incubator, which caused the cyanosis to disappear and normal respirations on the next day.

On October 6th when the patient was being nursed he suddenly developed considerable redness all over the right half of the body, with sharp delimitation in the median line. Changing the child's position did not influence the condition. The redness persisted for two hours. The left half of the body was paler than normal as compared with the right. The pupils were equal and reacted to light. Otherwise no signs of cerebral lesion. The temperature was normal.

During the continued stay in hospital the infant presented no deviations from the normal course for a premature infant. He was discharged well on November 8th.

The boy was subsequently re-examined, for the last time on December 10th, 1951, and was reported to have developed normally, and did not present any signs of cerebral injury.

Case 4. A boy, born on December 12th, 1949, a fortnight before full term. The mother a para III. The infant was born by caesarian section, because of pregnancy albuminuria with high blood pressure. Birth weight 3100 g. The infant was cyanotic in the peripheral parts of the body, and his temperature did not exceed 34.4° C. He was transferred to the Children's Hospital on December 13th. On admission there was considerable cyanosis round the mouth and on hands and feet. The temperature was subnormal. The respiration normal. The large fontanelle was not tense, nor were there any other signs of cerebral injury. Inner organs normal. He received oxygen and was put to bed with a hot-water bottle and heat pad, after which the temperature soon became normal and the cyanosis subsided.

On the whole his condition improved, but for a couple of weeks there was some stupor, and he failed to gain weight. After administration of phenoprominsulfate he became much livelier and gained weight.

On January 9th when the patient was examined with a view to being discharged home he suddenly developed pallor all over the left half of the body with very sharp delimitation in the median line, whereas the right half of the body was vividly red, probably with a little heightened colour than before the crisis. Alteration of the child's position did not influence the change which soon disappeared, recurring, however, after a while and persisting for some minutes. He presented nothing abnormal at all. A neurological examination disclosed nothing pathological.

On January 10th the patient was discharged well. A week later the mother phoned and reported that the boy had had an additional attack of unilateral pallor, obviously of the same nature as that in the hospital. He presented besides nothing abnormal and developed well. Re-examination on September 4th, 1952, revealed no sequelae of cerebral injury.

Apart from the sudden unilateral change of the skin colour, a feature common to the four cases described, the patients were in a state of universal cyanosis at birth and during the initial postnatal period. In case 1 there were also twitchings of the mouth to begin with, and the 4th patient exhibited some stupor for a few weeks after birth. The other two were prematures. In all the cases there were thus special reasons for watching for the possibility of a brain lesion. The vascular crisis in the form of vasoconstriction or vasodilatation in the skin, which was observed in the infants, was probably due to a central impulse, as it involved the entire half of the body in each case. In the first place, attention is focused on the suprasegmental autonomic centers in the medulla and the hypothalamus. An unilateral vasoconstriction may be induced experimentally through irritation of the vasomotor centre in the medulla oblongata on either side. It has been possible to produce the same effect in the hypothalamus and also from certain portions of the hemispheres in dogs. Being aware of the tendency to microscopical brain lesions which, as described above, is characteristic in the newborn, and in view of the fact that these lesions often seem to cause quite insignificant symptoms, the author believes it is most natural to assume that the vascular crises in our cases are associated with similar lesions in or near the medullary (or hypothalamic) centres mentioned. In the absence of other irritation symptoms in our cases a location to the hemispheres is perhaps less probable. The relatively sudden onset and disappearance, respectively, of the skin symptoms are probably suggestive of a local vasospastic factor causing the symptoms centrally. The probable mechanism of the unilateral changes will then be that a sudden vascular spasm, on account of an irritation from the primary lesion, occurring within the area of the vasomotor center on one side of the medulla. Thus the circulation to this area is checked, the content of carbonic acid increases and the centre is irritated. As mentioned, it is possible that the primary lesion is located higher up, in the hypothalamus. However, since it should induce a vascular spasm in this case as well, these centres ought to be sensible to carbonic acid, if the unilateral colour effect is to appear.

In certain acute lesions of the medulla unilateral sweating has not infrequently been observed (FORD). The fact that the autonomic symptoms in our cases are unilateral is thus parallelled clinically with a medullary location of the injury. In one of our cases sudden and inexplicable oscillations of temperature were observed on the very day of the vascular crisis. Hyperthermia and hypothermia are hypothalamic symptoms. It is not impossible that the injury in this case was located to this portion of the brain.

Summary

The causal mechanism of two types of cerebral birth injury — hemorrhages and the hypoxemic ganglion cell lesions — is discussed in connection with four cases of unilateral skin vessel crises in infants during the first months of life. At birth and during the initial postnatal period all the infants had been in a state of universal cyanosis, but, with one exception, they did not present any signs of a brain lesion. Within a period of 4 to 28 days after birth sudden attacks of severe pallor or redness occurred all over one half of the body, with sharp delimitation in the median line. The author has not been able to find similar observations in the literature. It is thought to be due to minor brain lesions occurring during delivery and located in or near the suprasegmental autonomic centres in the medulla or the hypothalamus.

Crises vasculaires cutanées unilatérales chez le nouveau-né.

Le mécanisme causal des deux types de lésions cérébrales observées à la naissance (hémorragies et lésions par hypoxémie des cellules ganglionnaires) est discuté, par rapport à 4 cas de crises vasculaires cutanées unilatérales, survenues chez des enfants, dans les premiers mois de la vie. Tous les enfants ont présenté une cyanose généralisée à la naissance, et dans la période post-natale qui suit immédiatement. A l'exception d'un seul, ils n'ont présenté aucun signe de lésion cérébrale. Au cours d'une période de 4 à 28 jours aprés la naissance, ils ont présenté de brusques accés de pâleur accentuée ou de rougeur, dans toute une moitié du corps, avec une délimitation exacte au niveau de la ligne médiane. L'auteur n'a pas trouvé d'observation similaire dans la littérature. Il pense que ces phénomènes sont dus à de petites lésions cérébrales produites au cours de l'accouchement, et situées dans les centres autonomes de la moëlle ou de l'hypothalamus, ou près de ceux-ci.

Halbseitige Hautgefässkrisen beim Neugeborenen.

Es wird über 4 Fälle von halbseitigen Hautgefässkrisen berichtet, die bei Säuglingen in den ersten Lebensmonaten auftraten. Im Zusammenhang damit werden zwei Arten von cerebralem Geburtstrauma, — Blutungen und hypoxämische Ganglienzellschädigungen, und ihr ursächlicher Mechanismus besprochen. Bei der Geburt und im Anfang der postnatalen Periode befanden sich alle Säuglinge in einem Zustand genereller Cyanose, zeigten aber mit nur einer Ausnahme keine Symptome einer Hirnschädigung. In einer Zeitspanne von 4 bis 28 Tagen nach der Geburt traten plötzliche Anfälle von intensiver Blässe oder Röte auf, die die eine Körperhälfte betrafen und scharf in der Mittellinie begrenzt waren. Der Verfasser hat keine ähnlichen Beobachtungen in der Literatur auffinden können. Was die Ätiologie betrifft, so vermutet man, dass kleinere, während der Geburt auftretende, Hirnschädigungen in den suprasegmentalen autonomen Zentren oder ihrer Nähe oder im Hypothalamus verantwortlich zu machen sind.

Crisis cutaneas unilaterales en el Recien Nacido.

La causa y mecanismo de dos tipos de injuria cerebral al nacer (hemorragias y lesiones hipoxémicas de las celulas ganglionares) se discuten en conexión con los 4 casos de crisis unilaterales de los vasos de la piel en niños durante el primero mes de vida. Al nacimiento y durante el período postnatal inicial todos los niños han estado en un estado de cianosis universal, pero, con una excepción, no presentaron ningun signo de lesion cerebral. En un período entre 4 y 28 días después del nacimiento sorpre-

sivos ataques de palidez intensa y enrojecimiento ocurrieron en una mitad del cuerpo con exacta delimitación en la línea media. El autor no ha sido capaz de encontrar observaciones similares en la literatura. Se piensa que se debe a lesiones cerebrales menores que ocurren durante el parto y localizadas en o cerca de los centros medulares autonómicos suprasegmentales o en el hipotalamo.

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Received 2.12. 1952.

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Acta Pædiatrica **42**: 514—519. Nov. 1953

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The Cocarboxylase Content of the Blood in Children

by C.-E. RÄIHÄ and O. FORSANDER

Investigations on vitamin B_1 have been extensive since it was discovered at the end of the last century. Since then, knowledge about it has steadily progressed, until LOHMAN in 1937 showed its physiological significance as part of the coenzyme in the ferment cocarboxylase.

Thiamine deficiency causes serious disturbances in different parts of the organism. For this reason it has been considered highly important to know about the vitamin level. Experiments have shown that the thiamine content of tissues and blood reflects the vitamin content in food. By examining the thiamine content in blood or in its phosphorylated form, cocarboxylase, it can be shown whether the individual in question has to be supplied with the vitamin. Unfortunately, however, a clear decrease of the thiamine content is apparent only when other physiological changes have already started in the organism.

Blood does not normally contain free thiamine in any remarkable quantities, only its phosphorylated form cocarboxylase. The cocarboxylase is bound to the protein of the blood cells and is not found in the plasma. If the cocarboxylase appears in the plasma it is rapidly dephosphorylated by the phosphatases to free thiamine, and is either excreted in the urine or reabsorbed and rebuilt in some other cells to cocarboxylase once more.

Method

As blood contains cocarboxylase in small amounts only, a sensitive method is required if small quantities are to be analysed. For our work we chose WESTENBRINK's manometric method because it is sensitive enough to allow double-analyses from 4 ml of blood. In experiments with infants we only made single analyses from 2 ml of blood. The blood sample was drawn from an arm vein with a syringe which contained 0.2 ml of potassium oxalate solution as anticoagulant. We used alkaline-washed Oranienboom brewers' yeast as apocarboxylase for the manometric determination in the Warburg apparatus. The Finnish yeast we tried did not prove to contain enough active enzyme after the alkaline washing. A control experiment with certain known amounts of cocarboxylase was always performed simultaneously: it appeared that the reading of the manometers varied in each experiment because the alkaline washing of the yeast could not be performed under absolutely identical circumstances. Fig. 1 shows a typical control curve.

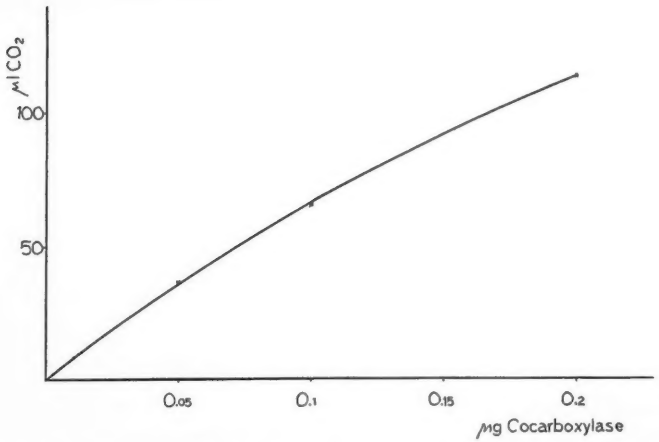

Fig. 1. The development of CO_2 in control experiments with known amounts of cocarboxylase.

Results and Discussion

At the Children's Clinic in Helsinki we investigated the cocarboxylase content in blood from children of different ages in 120 cases. The blood samples were drawn from children without any clinical symptoms of vitamin B_1 deficiency. The entire material is collected in Fig. 2. The thick line marks the average value, µg cocarboxylase per 100 ml of blood, for each age group. The dotted area shows the values within which 90 per cent of our material falls. The blood samples at 0 years were drawn immediately after birth, directly from the cord blood. It is found from the average curve that the cocarboxylase content in blood is considerably higher for young children than for older ones and that it decreases with age. The greatest decrease takes place during the first year of life, but the decrease continues steadily until the age of 7 years. After this the cocarboxylase content is constant and decreases but insignificantly.

Fig. 3 shows how the cocarboxylase is distributed between mother and infant. The blood samples from the mother were drawn immediately after the birth, and from her infant from the cord immediately after birth, and also some days later. The cocarboxylase content for the mother is much lower than that for her infant, and even a little lower than the average for adults. This is in accordance with the results given by SLOBODY *et al.* These workers found in their experiments that the cord blood contained on an average 11.63 µg thiamine per 100 ml of blood while the mother's blood contained only 6.97 µg per 100 ml. The corresponding values in our experi-

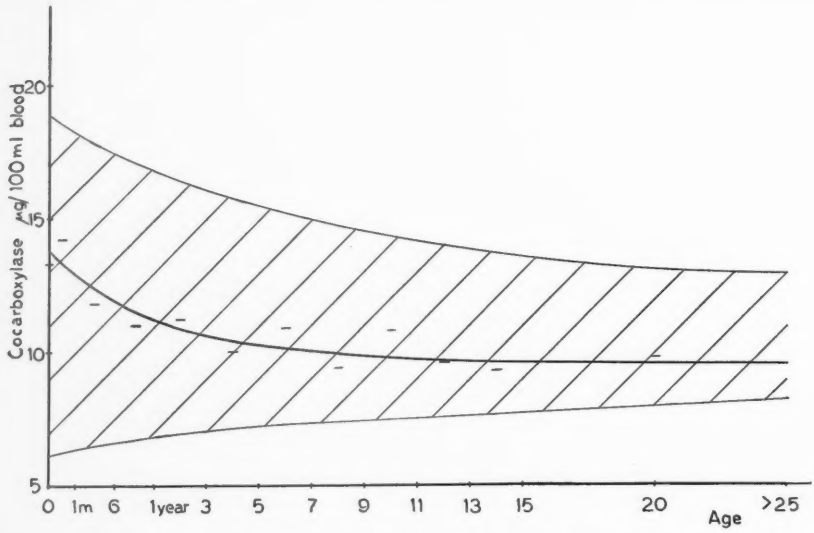

Fig. 2. The cocarboxylase content of blood at different ages. The dotted area shows the values within which 90 per cent of our material falls.

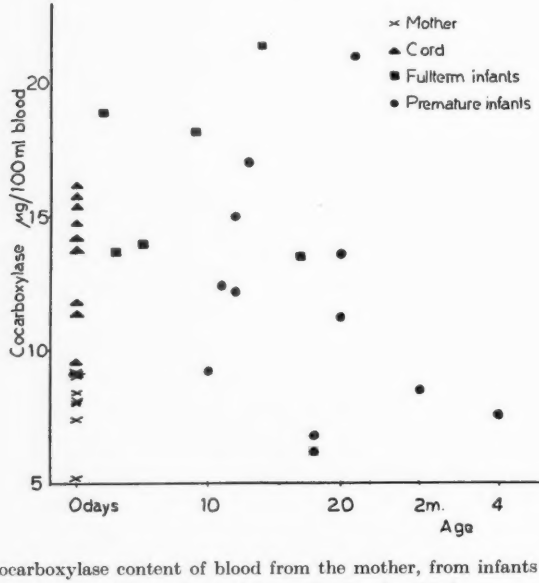

Fig. 3. The cocarboxylase content of blood from the mother, from infants a few days old, and from the cord immediately after birth.

TABLE I

The cocarboxylase content of blood for different ages.

Age	Number of investigations	Average value	Standard deviation
Newborn. . . .	11	13.3	2.1
0– 6 months .	29	13.3	4.5
½– 3 years . .	17	11.1	2.2
3– 7 „ . .	24	10.6	2.5
7–11 „ . .	10	10.2	2.8
11–15 „ . .	12	9.5	1.8
15–25 „ . .	16	9.8	1.6

ments are 13.7 μg cocarboxylase per 100 ml of blood and 8.1 μg, respectively. SLOBODY *et al.* also found that the thiamine content of blood decreased from 11.63 μg to 9.57 μg thiamine per 100 ml of blood during the first five days of life.

We cannot draw any conclusions from the material of our investigations because it is not extensive enough. Our experiments show, however, that the premature infants have a lower cocarboxylase content (about 10 μg) than the full-term infants (about 13 μg), during the two first weeks of life.

Table 1 contains the average values for the cocarboxylase content of blood for different age groups and the standard deviation from these values. The standard deviation is much higher for children under six months than for older ones. For newborn infants and for children older than six months it is, however, relatively constant.

Owing to the method used for determining the thiamine or cocarboxylase content of the blood, different results have been obtained. This is explained by the fact that the analysis methods are not completely specific for the substances in question, and impurities therefore interfere in part with the results of the analyses. Table 2 shows some results obtained from analyses of blood by employing different methods.

All these experiments were performed upon adults. In the experiments in which the total aneurin has been determined the results have, for comparison, been converted into μg cocarboxylase per 100 ml blood. By examining 20 adults WESTENBRINK *et al.* obtained an average figure of 11.2 ± 1.5 μg per 100 ml while our average figure for 16 adults is only 9.7 ± 1.6 μg per 100 ml, although we employed the same analysis method.

Almost all the cocarboxylase in blood is bound to the protein of the blood cells (SMITS *et al.*). The white blood cells contain about 200 times more enzyme than the red blood cells, but the red blood cells, due to their higher

TABLE II

The cocarboxylase content of blood analysed according to different methods.

Method	Substance determined	g per 100 ml	Author
Thiochrome . .	Total Aneurin	11.7	RITSERT
Phycomyces . .	,,	11.7	BANG
Manometric . .	Cocarboxylase	11.7	WESTENBRINK *et al.*
,, . .	,,	7.5	GOODHART *et al.*
Fermentation .	Total Aneurin	5.2	OLDHAM *et al.*

number, form the major part of the total cocarboxylase content of blood It could be supposed that variations in the haematocrit value of blood would be reflected in the cocarboxylase content. This is partly the case. But the haematocrit value decreases only during the first 15 days after birth (LUCAS *et al.*), after which it is relatively constant. The cocarboxylase content decreases, as mentioned above, until the age of 7 years. The number of erythrocytes is also higher for newborn infants than for older ones. The number of erythrocytes decreases during the first weeks. There is, however, a relatively good correlation between the number of red blood cells and the cocarboxylase content of the blood. Whilst the erythrocyte content of 2-days-old children decreases by about 11 per cent until the age of 5 years, the cocarboxylase content decreases by about 14 per cent. It may be assumed, however, that the variations prevailing in the cocarboxylase content for the different ages, and also the variations in the same age group, do not depend on the variations of the blood elements only, but that they originate from different physiological needs of enzymes. The pyruvic acid content decreases with age (TALLQVIST), and cocarboxylase is closely connected to the pyruvic acid metabolism.

Summary

The cocarboxylase content of blood in children has been investigated in 120 cases. The enzyme content decreases with advancing age up to 7 years and is thereafter constant. There seems to be a correlation between the cocarboxylase content of the blood at different ages and the blood picture. We feel, however, that metabolic factors interfere with this correlation.

Le taux de cocarboxylase dans le sang de l'enfant.

Le taux de cocarboxylase du sang chez l'enfant, a été étudié dans 120 cas. Le taux de l'enzyme décroit progressivement jusqu'à l'âge de 7 ans, et demeure constant par la suite. Il semble y avoir un rapport entre taux de cocarboxylase dans le sang, selon l'âge, et l'image sanguine. Des facteurs métaboliques interviennent probablement dans ce rapport.

Der Cocarboxylasegehalt des Blutes bei Kindern.

Der Cocarboxylasegehalt des kindlichen Blutes wurde in 120 Fällen untersucht. Der Enzymgehalt sinkt mit zunehmendem Alter bis zum 7. Lebensjahr und ist danach konstant. Es scheint eine Korrelation zwischen dem Cocarboxylasegehalt des Blutes in den verschiedenen Lebensaltern und dem Blutbild vorhanden zu sein. Wahrscheinlich sind jedoch auch Stoffwechselfaktoren bei dieser Korrelation mit im Spiele.

El contenido de cocarboxilasa en la sangre del niño.

El contenido en cocarboxilasa en la sangre del niño ha sido investigado en 120 casos. El contenido en enzima decrece al avanzar en edad hasta 7 años, siendo después de esta edad constante. Parece haber una correlación entre la cocarboxilasa contenida en la sangre a diferentes edades y el cuadro sanguíneo. Creemos, sin embargo, que factores metabólicos interfieren en esta correlación.

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This work was aided by a grant from the Juselius Foundation.

Received 22.12. 1952.

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Acta Pædiatrica **42**: 520—525. Nov. 1953

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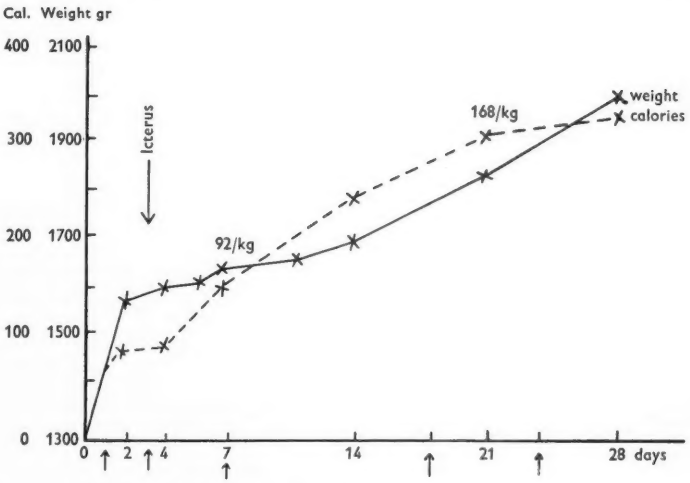
Pseudoprematurity

by BERTIL SÖDERLING

As is well known, the term *prematurity* is rather difficult to define. In my opinion, our attempts to estimate *maturity* from *weight* involve certain risks with regard to the practical treatment of low-weight newborns. Just as a 10-year-old child of normal intelligence may be at a stage of development that in no way conforms to its living age, a child of a weight at birth of less than 2500 g may have spent an intra-uterine period which does not fall below that of a fully developed child. Mostly, however, the stereotyped word "premature" elicits a plan of treatment which is standardized though differing from one place to another. A common feature of the various modes of treatment is that they have been designed for the type of weak child called premature or debile. This is analogous to the error of placing a child of ten in the wrong form at school. Imperceptibly, a hypothesis tentatively framed for the purpose of expressing the course of the maturity process in grammes has become a scientific reality.

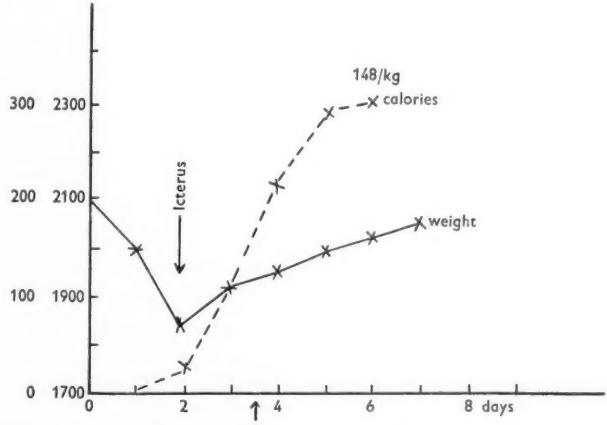
This applies not only to practical procedures in the case of a child termed premature but also to results recorded in connection with research, in various fields, from investigations of prematures. The majority of the scientists in question—they may be concerned with serologic problems, immunity, blood, vitamin or hormonologic questions—make no distinction between low weight and immaturity.

We have been disappointed in our attempts to determine the duration of pregnancy from information supplied by the mother on the last menstruation and from observations, if any, of foetal movements. This does not, of course, provide any justification for relying on weight as an indication of the duration of a pregnancy. Our knowledge of nutritive conditions during foetal life, and of the various causes that may conceivably affect the normal physical growth of a foetus, is far from sufficient. Considering that we have slipped away from earlier methods of determining the precise duration of pregnancy, i. e., that we find ourselves a little too far away from the obstetric findings and favour the simpler method of deciding the duration from the weight at birth. We often fail to apply *both*, and the term maturity has,



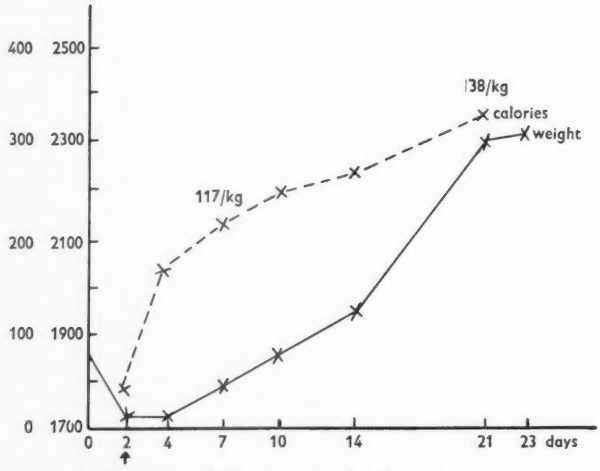
Feeding : bottle tube bottle-fed ad lib. put to breast ×3 ×6
Vomiting : VV V VV V V
Stools : I I III I III I IIII
Reg. of temp.: incubator bed + 1 + 0

Case 1. Last menstr. 3.VIII.50. Born 5.V.51. Birth weight 1 300 g.



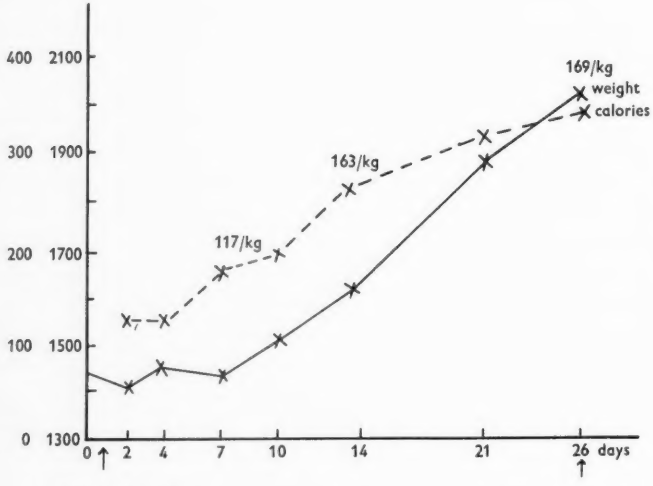
Feeding : bottle-fed ad lib. put to breast
Vomiting : VVV O
OOOO
Stools : II III IIII II II II I
Reg. of temp.: incubat. bed + 1 + 0

Case 2. Last menstr. end of May 51. Born 6.III.52. Birth weight 2 100 g.



Feeding : bottle-fed ad lib breast-fed ×3 ×5
Vomiting : O VV V
Stools : III III III III I II
Reg. of temp.: incub. bed. + 1 bed + 0

Case 3. Last menstr. 6.VII.51. Born 6.II.52. Birth weight 1 860 g.



Feeding : bottle-fed ad lib put to breast
Vomiting : V OO OO
Stools : I II III III I III II II
Reg. of temp.: incubator bed + 1 + 0

Case 4. Last. menstr. 23.VI.51. Born 25.III.52. Birth weight 1 440 g.

to an *unnecessary extent*, been left hanging in the air. The result is, in practice, a vicious circle: the weight at birth is low, hence a child is immature or not sufficiently developed—and it is not fully developed because it weighs too little at birth.

At the Pediatric Clinic at Borås, we have in recent years observed and tried to analyse these questions from the point of view of ordinary practical treatment.

Generally speaking, our aim has been to ascertain the degree of maturity by other means than physical measurements. In this connection, we have had recourse to the physical development, in this particular instance centring round the following question: Does the behaviour conform more to that of a fully developed newborn than to that of an underdeveloped foetus? It is, therefore, part of our first routine examination to try to ascertain approximately *where* the intra-uterine maturation process has been interrupted, and whether it can be considered to have been broken off too early. Here, *Gesell* has some important information to supply on the embryology of behaviour.

The behaviour is, *inter alia*, conditioned by motoricity, statics, series of reflex mechanisms, warding-off reactions, sound and light reactions, etc. We hope to be able to revert, on a future occasion, to this subject in a more comprehensive way. Clearly, the mental development can also, and perhaps most usefully, be studied from general behaviour, such as crying reactions, alertness, sucking capacity, etc.

In this connection, the desire to consume, i.e. the appetite, seems to me to constitute a fundamental part of the maturation process.

On the one hand, an overly rigid regime of feeding has on earlier occasions killed a few debile children who were forced to eat until overcome by vomiting, asphyxia or fatigue.

On the other hand, it seems to be equally certain that our hesitation to allow a child individually to decide the amount of food, according to its own desire, has resulted in unnecessarily long hospitalizations and delays, unnecessary under-nutrition and over-treatment. The tube-fed cases have, regrettably enough, still to be generalized. It is not for us, with our writing-desk notions, to prescribe how much a child of this or that type should increase in weight in order to satisfy spectators outside the box. Since we are ignorant of the cause of the low weight of a child, it is more important to observe how much a child goes up in weight and what it consumes in calories when given free scope for its appetite.

Incidentally, e.g. on such an occasion, it will sometimes be found that *a condition of undernutrition, in which a low metabolism maintains a low body temperature—in itself perhaps estimated as an ordinary sign of debility—*

will quite simply disappear. On more than one occasion, an unrestricted consumption has been found to render superfluous any extra sources of heat.

The purpose of the aforementioned observations is briefly as follows:

At the first signs of distinct sucking reflexes and hunger sensations in a so-called premature we must cease playing with providence in the matter of calories. Unfortunately, the position is quite different with regard to the tube-fed cases, since, in that instance, we are without any hints for feeding. After having ascertained, with all available means, *that two prematures of the same weight show quite different degrees of mental maturity, we must make every effort to trace clinical histories and clinical conditions with a view to finding explanations for the difference in maturity between the two weight companions.* Among other things, the placenta should be subjected to a special examination. We may then arrive at a more definite medical interpretation of the well-known fact that, for instance, one 1300-g infant is not like another infant of the same weight. In the first instance, an almost fully developed low-weight newborn is concerned, and in the other an undeveloped foetus.

From a practical point of view, the essential thing is that these two different types demand an entirely different treatment, a fact of which experienced and sensible nurses are well aware. This does not introduce a new factor in investigating pseudomaturity, for the care of prematures requires in any case a specially trained and experienced staff.

The aforementioned observations are illustrated by graphical curves from four cases.

Summary

The importance of distinguishing between prematurity and pseudoprematurity is stressed. The author criticizes the practice of equalizing low weight and immaturity. This is important from the point of view of theoretical research, and no less from that of practical treatment. A desire to consume is often suppressed, and various delays in development (e.g., in the capacity to regulate the body temperature) will then result. Teamwork research regarding the origination of pseudoprematurity should be intensified.

Pseudoprématurité.

L'auteur attire l'attention sur l'importance qu'il y a à distinguer prématurité et pseudoprématurité. Il critique l'usage pratique qui égalise faible poids et maturité insuffisante. Ceci est important des points de vue des études théoriques et de traitement pratique. Un besoin de consommation accrue est souvent réprimé et il en résulte des retards variés du développement (pour exemple concernant la régulation thermique). Un travail princeps concernant l'étiologie de la pseudoprématurité doit être poussé.

Pseudofrühreife.

Die Bedeutung des Unterschiedes zwischen Frühreife und Pseudofrühreife wird betont. Der Autor kritisiert die gebräuchliche Gleichsetzung von Untergewicht bei der Geburt und Frühreife. Dies ist vom Standpunkt der theoretischen Forschung als auch vom Standpunkt der praktischen Behandlung wichtig. Der Wunsch zur Nahrungsaufnahme ist oft unterdrückt und daraus resultieren verschiedene Störungen in der Entwicklung (z. B. in der Fähigkeit, die Körpertemperatur zu regulieren). Gemeinschaftsforschung in Bezug auf den Ursprung der Pseudofrühreife sollte intensiviert werden.

Seudopremadurez.

La importancia de distinguir entre premadurez y seudopremadurez es remarcada. El autor critica la costumbre de igualar bajo peso a inmadurez. Esto es importante desde el punto de vista de la investigación teórica así como del tratamiento práctico. Un deseo de consumir es amenudo suprimido, y varias detenciones en el desarrollo (por ej. en la capacidad de regular la temperatura del cuerpo) resultarán entonces. Debe intensificarse la investigación con team-work en lo que se refiere al origen de la seudopremadurez.

Received 16.1. 1953.

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Acta Pædiatrica **42**: 526—534. Nov. 1953

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Children of Diabetic Mothers

Electrocardiographic Studies in the Newborn

by STIG-IVAR BJÖRKLUND

The introduction of insulin decreased the frequency of infertility and of abortions due to diabetes mellitus in women (WHITE *et al.*, PATTERSON *et al.*). Foetal mortality is, however, still high (MORGAN, KRAMER, ALLEN, WHITE *et al.*, MILLER *et al.*).

Dyspnoea, apnoea, cyanosis and arrhythmia cordis are fairly common and sometimes fatal in the neonatal period in children of diabetic mothers (MILLER, WHITE, MILLER & WILSON). The cause of these disturbances is not properly understood.

Autopsies of children of diabetic mothers often reveal hyperplastic adrenals (MILLER, GRAY *et al.*, WHITE *et al.*, OKKELS *et al.*). Hyperplasia of the adrenals is usually believed to be associated with hyperfunction of the adrenal cortex.

MILLER and MILLER & WILSON supposed the symptoms in the neonatal period to be due to cardiac disturbance. ZIEGLER described pathological T waves in the electrocardiogram of a "normal" newborn child of a diabetic mother. SANFORD reported a diphasic T wave in a lead I tracing of a similar newborn child.

In an attempt to elucidate the underlying mechanism of the above-mentioned disturbances, the writer analysed serial electrocardiograms recorded in the neonatal period of such children.

The Author's Series

The series consisted of 15 children of diabetic mothers. Eleven of these children were examined at the Flensburg Children's Hospital in Malmö, and 4 of them at the Children's Hospital at Sundsvall. All of these children received oxygen during the first days of life. A control group consisting of 37 children with birth weights ranging from 2 800 g, to 5 500 g, was also examined electrocardiographically once or twice during the neonatal period. These controls had been born of non-diabetic mothers and had shown no signs of heart disease.

The three standard leads were used throughout.

Results

The electrocardiographic tracings of all of the controls were normal, as judged by data given by ZIEGLER, for example. In some, however, the Q-T intervals were short. The T waves were iso-electric or positive, apart from one exception where the T wave was slightly negative in the lead I tracing. S-T segments were on the iso-electric line. In view of the fact that it has not yet been made clear whether the formula for the relationship between the Q-T interval and the rate is also valid for high heart frequencies, this relationship is shown graphically in Fig. 1.

In 11 of the 15 children of diabetic mothers the electrocardiograms were abnormal. The changes consisted of suppressed or sagged S-T segments, pathologically negative T waves, prolongation of the Q-T intervals and pathological U waves (exemplified in Figs. 2, 3 and 4). Ventricular tachycardia was noted in 2 cases (cases 1 and 4; Figs. 5 and 6).

The relationship between the Q-T interval and the heart rate recorded in children of diabetic mothers was compared with that found in the controls (Fig. 1). Neither the length of gestation nor the duration of the diabetes was found to be related to the occurrence of pathological electrocardiograms or symptoms (Table 1). The series was, however, too small to permit valid conclusions.

It is clear from Table 1 that the electrocardiographic changes disappeared within about 15 days of life, usually within the first 5 days. It is also clear

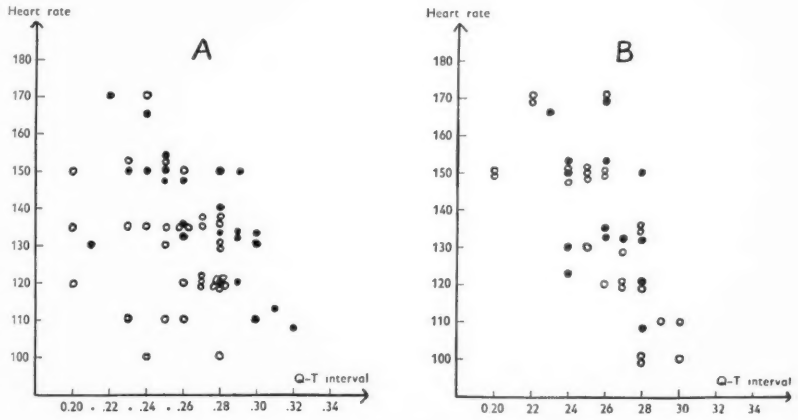
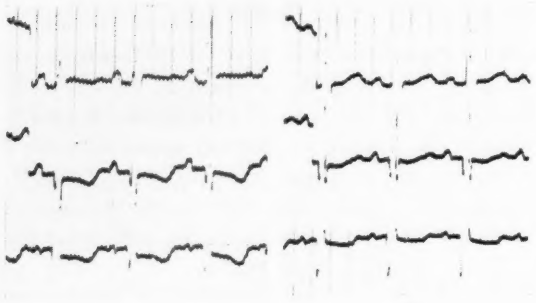
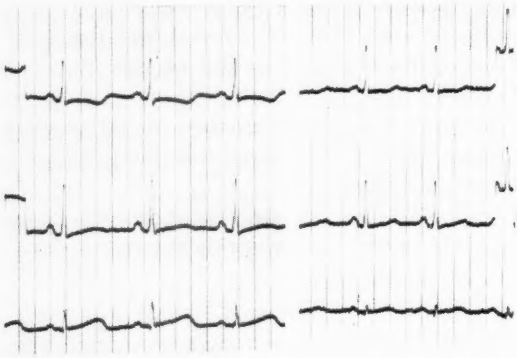


Fig. 1. A. Heart rate: Q-T interval. Age 0–3 days. ● represents 14 children of diabetic women. ○ represents 33 children of non-diabetic women. B. Heart rate: Q-T interval. Age: 4–15 days. ● represents 11 children of diabetic women. ○ represents 25 children of non-diabetic women.



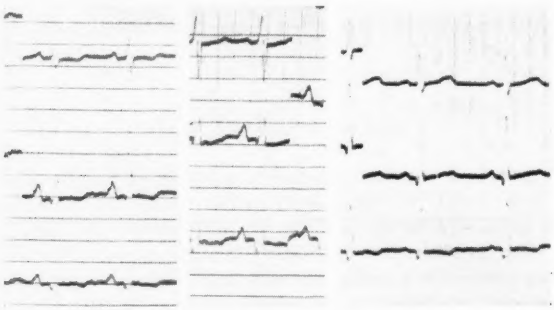
A B

Fig. 2. Case 8. A. One day old. Depressed S-T segments in lead 2 and 3. Pathological T waves in lead 2 and 3. B. 15 days old. Normal electrocardiogram.



A B

Fig. 3. Case 12. A. One day old. Depressed S-T segments in lead 1. Sagged S-T segments in lead 2. Negative T waves in lead 1. B. 22 days old. Normal electrocardiogram.



A B C

Fig. 4. Case 15. A. 7 days old. Depressed S-T segments in lead 1. Negative or diphasic T waves in lead 1 and 2. B. 12 days old. Sagged S-T segments in lead 1 and 2. Pathological T waves in lead 2, U wave? C. 2 months old. Normal electrocardiogram.

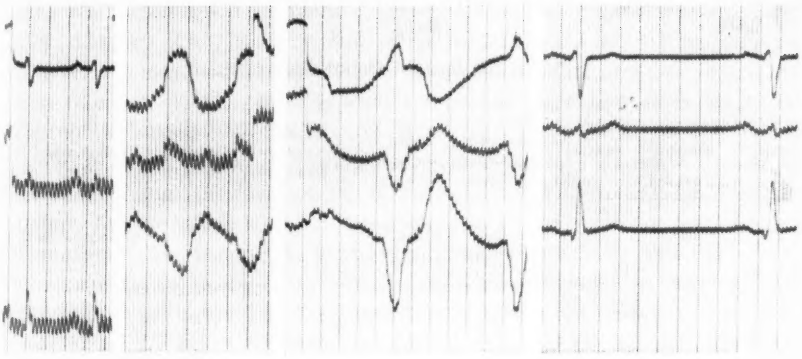


Fig. 5. Case 1. A. 4 hours old. P waves present. No T waves visible. B. 12 hours old. "Ventricular tachycardia". C. 15 hours old. "Exhausted heart muscle". D. 17 hours old. In extremis. Bradycardia.

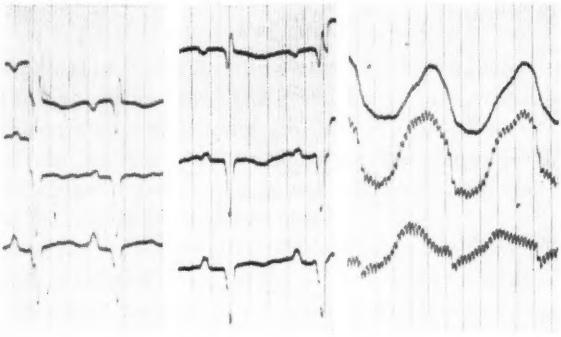


Fig. 6. Case 4. A. 6 hours old. Dextrocardia. Negative T waves in lead 2. B. 11 hours old. Negative T waves in lead 2 and 3. U waves in lead 2 and 3? C. 31 hours old. 15 minutes before death. "Ventricular tachycardia."

that in 10 cases with abnormal electrocardiograms the changes appeared during the first day of life. In case 15 no electrocardiograms were traced during the first 6 days.

Electrocardiographic changes were observed both in the presence and in the absence of such disturbances as collapse, cyanosis, arrhythmia or dyspnoea, but in none of the children with any of these disturbances was the electrocardiogram normal.

TABLE I

15 children born of diabetic mothers.

Case	Birth weight in grams	Gestation period in weeks	Mother's diabetes duration in years	Age of child at examination	ECG −normal +pathol.	Clinical disturbances	Autopsy
1	1 250	32	11	6 hrs.	+	+	Subaortic defect
				1 day	+	+	
2	2 320	36	23	6 hrs.	−	−	
				3, 11 days	−	−	
3	2 660	31	11	6 hrs.	+	+	Immaturity
				1 day	+	+	
4	2 800	36	13	4 hrs.	−	−	Cor triloculare
				9 hrs.	+	−	
				28, 30 hrs.	+	+	
5	3 430	35	5	1–2 days	+	−	
				3 days	+	+	
				5 days	−	−	
6	3 900	36	7	6 hrs.	−	−	
				1 day	+	−	
				2 days		+	
				5 days	−	−	
7	3 920	36	2/12	6 hrs.	−	−	
				1–5 days	−	−	
8	3 950	34	2/12	1 day	+	+	
				3, 5 days	+	−	
				9, 15 days	−	−	
9	3 980	35	8	4 hrs.		+	
				1, 2 days	+	−	
				8 days	−	−	
10	4 070	42	6	4 hrs.	+	−	
				2 days	−	−	
				6 days	−	−	
11	4 320	37	2/12	1, 2, 4 days	−	−	
12	4 620	39	11	1, 2 days	+	−	
				3–15 days	+	−	
				22 days	−	−	
13	4 730	36	2	4 hrs.	+	−	Aspiration
				1 day		+	
14	4 850	?	3	2, 9 days	−	−	
15	5 250	38	1	4 hrs.		+	
				1, 3 days		+	
				7 days	+	+	
				10 days		+	
				12 days	+	−	
				2 months	−	−	

As the pathological electrocardiograms suggested hypopotassemia (STOLL *et al.*, BELLET *et al.*, MARTIN *et al.*, TARAIL, BELLET *et al.*) the serum potassium was determined on the first or second day of life in a few of the children (cases 4, 6, 11, 14). The values recorded were 19.6, 16.3, 21.2, 21.4 mg/100 ml, respectively. MCCANCE gives 30.6 mg/100 ml, as the normal value for serum potassium during the seventh to the fourteenth day of life. KOTIKOFF found the level of serum potassium in children to be 20–25 mg/100 ml, but he did not include the determinations made during the first 2 months of life because he found these values extremely high. The serum potassium levels found in the present series were probably below normal.

In case 4 the excretion of 11-oxysteroids during the first 24 hours of life was 0.23 mg (SPRECHLER), which was apparently high. In cases 1 and 4 there was ventricular tachycardia, and death was probably caused by damage to the heart muscle. In case 1 the autopsy revealed a very small sub-aortic defect of the septum, but this was surely not the cause of death. In case 4 the infant had cor triloculare. Death in case 3 was probably due to the immaturity of the child, and in case 13 to aspiration demonstrated at autopsy.

Discussion

The electrographic changes suggest myocardial damage and resemble those found in hypopotassemia. The alteration of the potassium metabolism and hence the cardiac disturbances are probably the result of the hormonal imbalance in the diabetic mother. Since our knowledge of the physiology of children of diabetic mothers is, as yet, rather scanty, the following discussion must be highly speculative.

As mentioned above, these children often have adrenal hyperplasia. Sometimes (MILLER, NEVINNY *et al.*, OKKELS *et al.*, SMYTH *et al.*) the pituitary contains an increased number of eosinophils, in others the bone age is advanced (WHITE). All of these findings are compatible with increased hypophyseal activity and secondary hyperplasia with hyperactivity of one or more of the functions of the adrenal cortex.

During intra-uterine life the foetus obtains sufficient electrolytes and glucose from the mother. Foetal adreno-cortical dysfunction with increased production of the so-called electrolyte hormone may be of minor importance because of the free passage of electrolytes between the mother and the foetus. If this foetal dysfunction with increased production of the electrolyte hormone continues for some time into the neonatal period without supplementary electrolytes, the blood potassium is lowered.

It is well known that these children are often heavier at birth than other children and that they have a peculiar, oedema-like appearance. It seems possible that this high birth weight is partly due to retention of water and

sodium with a concomitant increase in the excretion of potassium—an effect of increased production of electrolyte hormone.

Earlier it was believed that hypoglycemia was responsible for the above-mentioned disturbances in the neonatal period of these children. This hypothesis is no longer accepted (WYNNE-JONES, MILLER, WHITE *et al.*, MILLER & WILSON, POTTER *et al.*). These children often have hyperplasia of the islands of Langerhans (MILLER *et al.*, POTTER *et al.*, MILLER, SMYTH *et al.*, NEVINNY *et al.*), but many investigators deny any relationship between this hyperplasia and increased insular function on the grounds that the blood sugar level in these children is not lower than in children of non-diabetic mothers and that the blood sugar increases during fasting. The difference in blood sugar values between the newborn and the mother during labour is greater if the mother has diabetes mellitus (PEDERSEN). It seems strange that the decrease in blood sugar does not produce blood sugar values of a hypoglycemic level. The possibly high value of 11-oxysteroids in case 4 can probably explain this: the effect of insulin is inhibited by an increased production of glucocorticoids.

Although the serum potassium was low in cases 6, 11 and 14, the electrocardiograms were normal. The serum potassium does not, however, reflect the cellular concentration of potassium, and it is known that it is the latter which is of importance to the heart muscle (WEISSBERG *et al.*, CURRENS *et al.*). It is possible that the low values for serum potassium with normal electrocardiograms indicate that too little potassium was available and that the potassium had already entered into the cells. A low serum potassium value is compatible with a normal intracellular concentration (MARTIN *et al.*). This discrepancy between the low serum potassium values and the normal electrocardiograms may, of course, also be due to the fact that the electrocardiographic changes are not the result of hypokaliemia. MILLER *et al.* called attention to the possibility that the increased storage of glycogen in the heart muscle may be the cause of the disturbances in the neonatal period. HEGGLIN *et al.*, in experimental investigations on the rat, could not, however, find any relationship between prolongation of the Q-T interval and the glycogen content of the heart muscle.

In cases 1 and 4 there was ventricular tachycardia. This is sometimes seen in hyperpotassemia. The preceding electrocardiograms with P waves and normal or lowered T waves are evidence against hyperpotassemia as the cause of the ventricular tachycardia in these 2 cases (WINKLER *et al.*).

As regards therapy, it is useful to perform balance studies of electrolytes and investigations of the excretion of the adrenal hormones before prescribing treatment. It seems, however, justifiable to administer potassium parenterally to the children with pathological electrocardiograms, if the electrocardiograms can be traced at relatively short intervals.

Summary

In the belief that the adrenal hyperplasia often seen in the children of diabetic mothers is associated with hyperfunction of the adrenal glands and that it may disturb the electrolyte balance and thereby also disturbs cardiac function, 15 children of diabetic mothers were examined. The investigation included an analysis of serial electrocardiograms traced in the neonatal period. In 4 cases the serum potassium was also determined. Abnormal electrocardiograms were seen in 11 cases. The electrocardiographic changes resembled those seen in hypopotassemia. The cause of this disturbance of the electrolyte metabolism is discussed.

Enfants nés de mères diabétiques. Études éléctrocardiographiques chez les nouveau-nés.

15 enfants de mères diabétiques furent examinés en se basant sur l'hypothèse suivante: l'hyperplasie surrénalienne est peut-être associée à une hyperfonction de ces glandes qui peut troubler l'équilibre éléctrolytique et secondairement les fonctions cardiaques. L'auteur analyse une série d'ECG enregistrés pendant la période néo-natale. Le potassium fut dosé dans 4 cas (potassium sérique). Dans 11 cas le tracé fut anormal, rappelant les modifications connues dans l'hypokaliémie. L'auteur discute les causes de ce trouble éléctrolytique.

Kinder diabetischer Mütter. Elektrocardiographische Untersuchungen beim Neugeborenen.

Im Glauben, daß die Nebennierenhyperplasie, wie sie oft bei Kindern diabetischer Mütter gesehen wird, mit einer Hyperfunktion der Nebennieren verbunden ist und diese das Elektrolytgleichgewicht und dadurch auch die Herzfunktion stören könnte, wurden 15 Kinder diabetischer Mütter untersucht. Die Untersuchung schloß eine Serie von Elektrocardiogrammen in der Neugeborenenperiode ein. In 4 Fällen wurde auch der Kaliumgehalt des Serums bestimmt. Abnorme Elektrocardiogramme wurden in 11 Fällen gefunden. Die elektrocardiographischen Veränderungen erinnern an jene bei Hypopotassämie. Die Ursache der Störung im Elektrolythaushalt wird diskutiert.

Niños de madres diabéticas. Estudios electrocardiográficos en el recién nacido.

En la creencia de que la hiperplasia adrenal que se ve amenudo en los hijos de madre diabética está asociada con hiperfunción de las glándulas suprarenales y que puede causar disturbios en el balance electrolítico y por tanto tambien disturbios en la función cardíaca, 15 niños de madres diabéticas fueron examinados. La investigación incluye un análisis de una serie de electrocardiogramas trazados en el período neonatal. En 4 casos el potasio en el suero fué también determinado. Electrocardiogramas anormales se observaron en 11 casos. Los cambios electrocardiográficos se parecen a los que se ven en la hiperpotasemia. La causa de el disturbio del metabolismo electrolítico es discutida.

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Received 20.1. 1953.

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Acta Pædiatrica **42**: 535—539. Nov. 1953

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A Creatinin Tolerance Test for Renal Function

by ALFRED SUNDAL

Clearance tests for renal function are dependent both on blood samples and on the meticulous collection of urine at certain time intervals. It is difficult to carry this out in infants and small children who cannot void at will and also in boys with no urinary infection whom it is inadvisable to catheterise. Furthermore, specimens obtained even after catheterisation in cases of hydronephrosis, megaloureter and other congenital malformations of the urinary tract do not necessarily represent the urine passed by the kidneys over a given time.

In 1935 the present author described a kidney function test based on the blood creatinin curve after an oral creatinin load, a test not dependent on urine collection and thus of special value in the pediatric clinic. Normally the endogenous creatinin excretion is fairly constant at about 1 mg per cent and dependent mostly on the muscle mass. Earlier investigators (EKEHORN, REHBERG) have shown that creatinin clearance is a satisfactory test of kidney function, and as creatinin is filtered through the glomeruli and also secreted from the tubule cells, the test gives information on the function of the whole nephron.

The blood creatinin curve depends on the ability of the kidney to excrete creatinin, and the fall in the blood creatinin values will reflect the kidney function in the same way as a creatinin clearance test after oral load. The blood creatinin curve, as also exogenous creatinin clearance, however, have a limitation as kidney function tests in oedematous patients. Here the creatinin load will give invasion of creatinin to the interstitial fluid, and the excretion from the kidney thus retarded will give a false indication of impaired kidney function.

The oral dose of 50 mg creatinin per kilo bodyweight is based upon the average weight for the patients' height, for this gives a more regular curve than when the dose is based upon the actual weight. The creatinin is rapidly absorbed and blood levels are at their highest after about one hour; thereafter the decrease is uniform until at about seven hours all exogenous creatinin is excreted. Plasma creatinin determinations are made 2 hours and 6 hours after the oral load. The difference between the two values as a per cent of the value 2 hours after the initial dose, gives a numerical expression of the ability of the kidney to excrete creatinin.

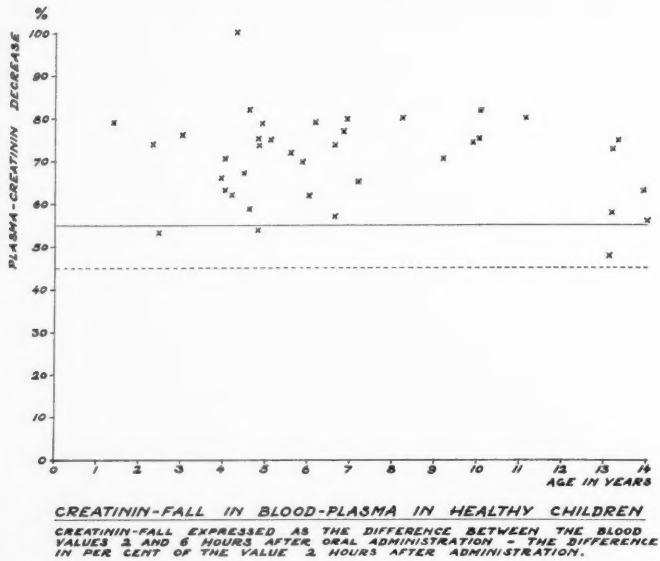
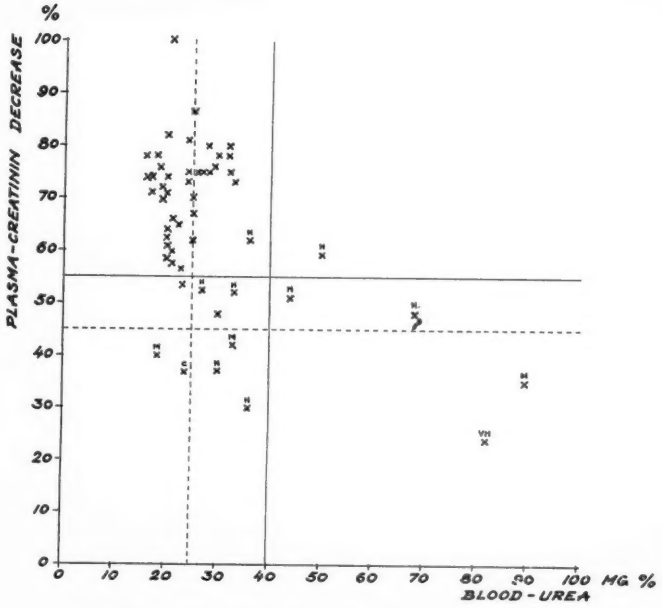


Fig. 1.

Method: At 7 o'clock 50 mg creatinin in 5 ccm water per kilogram average weight for the height is given to the fasting patient. Half an hour later a light breakfast, and later ordinary diet, is given. Blood samples are taken after 2 hours and 6 hours, i.e. at 9 o'clock and 1 p.m. One ccm of plasma is required, but since duplicate readings are desirable, 5 ccm of blood should be taken. The blood is deproteinised with saturated picrinic acid, and the filtrate added to sodium hydroxide gives a characteristic colour (the same as Jaffe's test) for colorimetric estimation. (For a more detailed description see SUNDAL, 1935.)

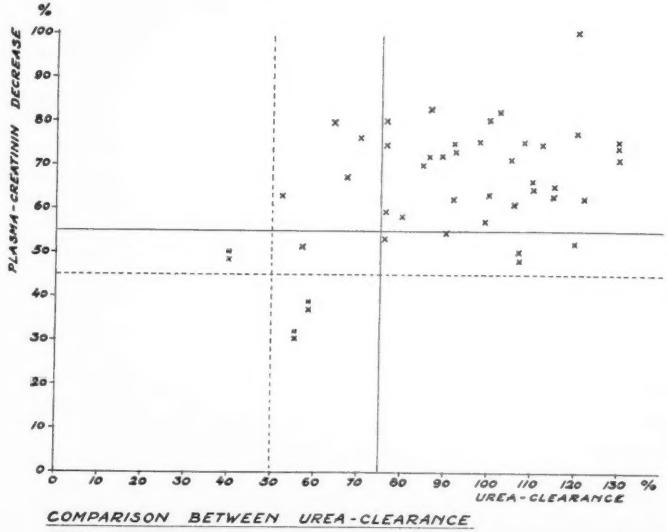
Fig. 1 shows the excretion of exogenous creatinin in healthy children at different ages. As might be expected the values vary considerably. The normal range has been established by comparing the normal values with values obtained in cases of known decreased kidney function. In this way it can be established that values for non-oedematous patients above 55 % are normal, those between 45 % and 55 % are borderline, and those below 45 % are abnormal.

Fig. 2 compares the creatinin fall and blood urea in healthy children and in patients with urinary and/or kidney disease. In general, decreased creatinin excretion corresponds with a high blood urea. But the creatinin test in kidney and urinary diseases shows some cases with low values, but a normal blood urea.



COMPARISON BETWEEN CREATININ-FALL IN BLOOD-PLASMA AND BLOOD-UREA.

Fig. 2. M = megalo-ureters (bilateral), N = nephritis, VN = renal thrombosis, C = renal rickets with cystinosis.



COMPARISON BETWEEN UREA-CLEARANCE AND CREATININ-FALL IN BLOOD-PLASMA.

CREATININ-FALL EXPRESSED AS THE DIFFERENCE BETWEEN THE PLASMA VALUES 2 AND 6 HOURS AFTER ORAL ADMINISTRATION - THE DIFFERENCE IN PER CENT OF THE VALUE 2 HOURS AFTER ADMINISTRATION.

Fig. 3.

Finally, simultaneous creatinin fall and urea clearance tests are performed, and as seen from Fig. 3 these two tests are closely related in most patients. These two different kidney function tests do not of course necessarily follow each other, for the active transport of urea and creatinin through the tubule cells is different.

Summary

The creatinin slope in blood plasma after an oral creatinin load is a test which gives important information about kidney function. Without needing urine collection—a procedure often difficult in infants and also in some cases with urinary disease even when collected by catheter—the blood creatinin fall gives values corresponding to the exogenous creatinin clearance test, and also to the endogenous creatinin clearance test, provided the patient is not in a pre-oedematous or oedematous stage. The author gives the values for creatinin fall in the blood in healthy children and in patients with decreased kidney function after an empirically chosen creatinin load.

Un test de tolérance à la créatinine pour l'étude de la fonction rénale.

La courbe de la créatinine dans le plasma, après la prise orale de ce produit, est un test donnant d'importants renseignements sur la fonction rénale. Pas d'obligation de recueillir les urines, ce qui est souvent difficile chez le nourrisson, et aussi dans quelques affections urinaires, malgré le sondage. La chute du taux de créatinine dans le sang fournit des données correspondant à un test de clearance à la créatinine exogène, et aussi à la créatinine endogène, à condition que le malade ne soit pas dans un état préœdémateux ou œdémateux. L'auteur donne les valeurs correspondant à la chute du taux de créatinine dans le sang chez des enfants bien portants, et chez des malades à fonction rénale diminuée, après la prise d'une dose empiriquement fixée de créatinine.

Ein Kreatinin-Toleranz-Test zur Nierenfunktionsprüfung.

Die nach einer oralen Kreatiningabe erhaltene Kreatininkurve im Blutplasma gibt wichtigen Aufschluss über die Nierenfunktion. Der Fall des Blutkreatinins ergibt Werte, die sowohl dem exogenen als auch dem endogenen Kreatinin-Clearance-Test entsprechen, vorausgesetzt dass sich der Patient nicht in einem prae-ödematösen oder ödematösen Stadium befindet. Das bei kleinen Kindern oft so schwierige Sammeln von Urin, oder auch das Sammeln via Katheter in einigen Fällen mit Nierenkrankheiten, sind bei diesem Test nicht erforderlich. Der Verfasser gibt Werte an für die Senkung des Blutkreatinins bei gesunden Kindern und bei Patienten mit herabgesetzter Nierenfunktion nach einer empirisch gewählten Kreatiningabe.

Un test de tolerancia a la creatinina para la función renal.

El índice de creatinina en el plasma sanguíneo después de la ingestión oral de creatinina es un test que da importantes informaciones alrededor de la función renal. Sin necesidad de juntar orinas (procedimiento amenudo difícil en niños y en algunos casos de enfermedades renales mismo cuando se obtengan por cateter), la caída de la creatinina en la sangre da valores correspondientes al « clearance test » de creatinina en-

dógena, siempre que no exista un estado preedematoso o edematoso. El autor da los valores de la caída de la creatinina en la sangre en niños sanos y en enfermos con disminución de la función renal. Estos valores son obtenidos de una carga empírica con creatinina.

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Received 26.1.1953.

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Acta Pædiatrica **42**: 540—541. Nov. 1953

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Active Basal Immunity and Its Application to Epidemiology

I. General Considerations

by HANS ERICSSON, LENNART HESSELVIK and BO VAHLQUIST

When planning immunization prophylaxis due consideration must be paid both to the prevailing epidemiological situation and to the type of protection afforded by the available immunizing technique.

Passive immunization is of use only for protection in situations with imminent threat of infection or when the disease in question carries a particularly heavy fatality risk, e.g. tetanus. The use of human serum is necessarily limited by the difficulties of producing such serum in sufficient quantity and with an adequate titre of antibodies.

Active immunization has a very wide range of indications. The criteria which must be satisfied are efficiency and a minimum of untoward side effects. Present-day preparations fulfil high requirements in the former respect but their use is still attended by a certain measure of unpleasant side effects. Active immunization is impracticable for hastily improvised prophylaxis. It requires systematic, long-term planning according to the epidemiological situation.

Against infectious diseases that appear only sporadically or have long ceased to cause widespread morbidity, complete protection may be deemed unnecessary. But a basal immunity, entailing a "secondary response" to repeated injections of the immunizing agent, may be both valuable and desirable in the event of a threatening epidemic. It is often very difficult, however, to secure public co-operation in a programme of immunization which, to the public as well as to medical personnel, lacks the stimulus of urgency. Under such circumstances it is particularly important to reduce the discomforts associated with the procedure and to strive for optimal results with a minimum of injections.

The combination of several antigens in one vaccine may be advantageous. The most topical disease risk should be stressed in public propaganda, even if the other components of the vaccine may, in the long run, be quite as important.

Practical Applications

The principles outlined above have been applied by the present writers in earlier work (ERICSSON, ERICSSON *et al.*, VAHLQUIST) with the long-term aim of introducing an immunization scheme which could secure a basal immunity against some of the most important infections of childhood. By application of the principle of secondary response to a booster dose, the basal immunity can rapidly be transformed into a satisfactory immunity according to the demands of the current epidemiological situation.

The practical applicability of these principles to tetanus prophylaxis has been proved experimentally by the work of ERICSSON (1948). When a basal immunity has been obtained the booster dose may, in injuries involving a risk of tetanus, replace passive immunization.

The following series of reports deals with the practical application of the same principles to diphtheria prophylaxis and with some other problems concerning the possibilities of making increased use of active immunization against the infectious diseases of childhood.

Summary

Some general immunological considerations and their practical application in immunization prophylaxis are discussed as an introduction to the following papers.

Immunité basale active et ses applications à l'epidémiologie. I. Considérations générales.

Considérations générales en immunologie et leurs applications pratiques dans le domaine de l'immunisation prophylactique. Ceci sert d'introduction à les études qui suivent.

Aktive Basisimmunität und ihre Bedeutung für die Epidemiologie. I. Allgemeine Betrachtungen.

Als Einführung in die folgenden Publikationen werden einige allgemeine Immunitätsprobleme und ihre Verwendung für die Immunisierungsprophylaxe diskutiert.

Inmunidad básica activa y su aplicación en la epidemiología. I. Consideraciones generales.

Se discuten algunas consideraciones inmunológicas y su aplicación práctica en la profilaxis de inmunización como una introducción a los siguientes artículos.

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Received 28.2.1953.

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Acta Pædiatrica **42**: 542—547. Nov. 1953

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Active Basal Immunity and Its Application to Epidemiology

II. Basal Immunity and Secondary Response in Diphtheria Prophylaxis

by HANS ERICSSON and LENNART HESSELVIK

The control of diphtheria was one of the epidemiological problems that assumed an important place in Sweden during the second world war. The incidence of the disease had shown a sharp decline in the interwar years, and the low record of 107 reported cases in a population of 6.5 millions was achieved in 1938. Concurrent with this decrease there was noted a very poor natural immunity as expressed by the percentage of nonreactors to the Schick test (ERICSSON and ERICSSON). The first years of the last war showed a moderate increase in the frequency of diphtheria. For this reason mass immunization of children was organized, and during 1944 sixty-eight per cent of all children under fifteen years of age were immunized.

The immunizing preparation used in this campaign had previously been found to effect Schick conversion with a single dose in more than 98 per cent of cases (ERICSSON 1943). For a detailed account of the 1944 programme, see ERICSSON and ERICSSON. Single-dose prophylaxis was therefore the basis of the 1944 campaign, and those of succeeding years followed similar lines.

By giving only one injection it was hoped to provide some degree of immunity for one year; a longer-lasting effect was not anticipated. (After eighteen months 57 per cent of the children were again Schick-positive.) The single injection was also intended to confer a basal immunity which should entail a more rapid response to diphtheria antigen, even after reconversion of the Schick reaction. Thus, in the event of a local or national epidemic, the basal immunity so conferred could rapidly be increased by a reinforcing or "booster" inoculation. The practical value and duration of this basal immunity, however, could not at that time be assessed with certainty.

It was considered desirable that the basal immunity should last for at least five years. Basal immunity should mean that a booster dose produces a sharp rise in the level of circulating antitoxin within ten days (this being a sufficiently short period to permit effective immunization in the event of an outbreak of the disease). A rise in the antitoxin titre which is, as far as hitherto known, the essential result of immunization against diphtheria with toxoid preparations, implies that the subject has at his disposal antitoxin with which to neutralize the toxic action of the infection. On the other hand, inoculation probably does not confer any direct immunity against the infection as such. Previously it was presumed that an antitoxin titre corresponding to the "Schick level" implied a satisfactory degree of protection. It has since been shown, however, that the antibody titre of the Schick level is not constantly 1/30 I.U./ml but varies in different subjects (JENSEN; VAHLQUIST and HÖGSTEDT).

This finding, and the desire to obtain an immunity as reliable as possible, would seem to necessitate the fixing of a higher titre as indicating "safe immunity" following active immunization. We have rather arbitrarily chosen the value 0.1 I.U./ml.

The investigation now presented was undertaken with the purpose of determining the value of the immunity remaining after a period of five years from the initial inoculation.

Material

From the municipal schools of Uppsala thirty-one children were selected at random among those whose records of previous diphtheria inoculation were complete and reliable. All of them had been immunized under the programme begun in 1944. None had had any known exposure to diphtheria since immunization. The general morbidity from diphtheria has been very low in Uppsala since 1944: only 58 cases (carriers included) have been notified in five years in a population of about 60,000. Most of these cases occurred in two children's homes.

The preparation used both for the initial and booster inoculations was identical with that described by ERICSSON (1946), except that the final washing of the precipitate was omitted. About 75 per cent of the active substance is adsorbed onto aluminium phosphate and the remainder is held in solution. Since this method renders the preparation suitable both for the initial inoculation and the booster dose, the use of a special fluid toxin recommended by American workers (LAPIN) for the booster dose is unnecessary.

Experimental

For their initial inoculation eighteen of the children had been given 0.5 to 1 ml of the immunizing preparation, i.e. 25 to 50 Lf. The other thirteen had received the same quantity on two occasions one year apart.

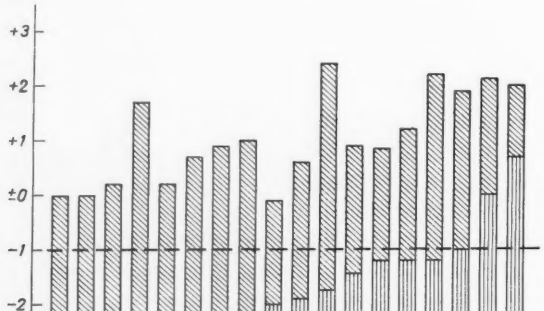
Five years after the last of these injections all the children were given 0.5 ml (25 Lf) of the same preparation.

The antitoxin titre was estimated (*a*) immediately before, and (*b*) ten days after the booster dose. Titrations were carried out on rabbits according to JENSEN's technique, and are presented in Figures 1 and 2.

Estimated as the level of circulating antitoxin five years after the last injection, basal immunity was obviously unsatisfactory in that many of the children had no demonstrable antitoxin titre, and in others the titre was very low. In the group whose first inoculation had been performed in two stages the titres found were somewhat higher than in the other group but were still unsatisfactory. The difference between the two groups has statistical probability.

The titration values were assigned to six categories—the distribution best suited to the technique and nature of the titration method used—and a variance analysis made. It was found that the probability of the difference between the two groups being due to chance lay between 0.01 and 0.05.

Judged by enhanced reactivity to the antigen, basal immunity was demonstrated by a sharp rise in the serum antitoxin titre in all the children



Titre of antitoxin before the booster dose
Rise in titre after the booster dose
---- Sensitivity limit of the titration method
—— Minimum antitoxin titre accepted by the writers as satisfactory

Fig. 1. Log_{10} of diphtheria antitoxin titre before and after a booster dose of toxoid. The primary immunization had been conferred with a single dose.

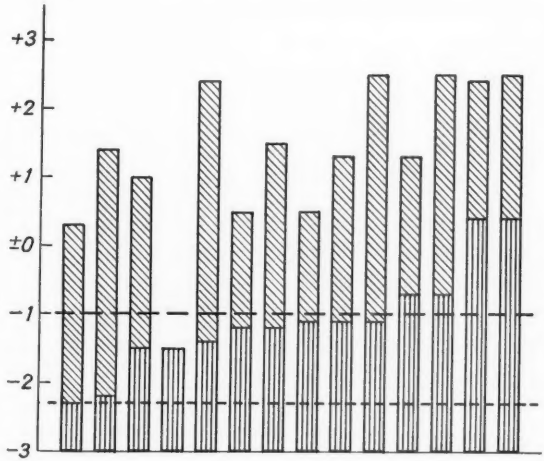


Fig. 2. Log_{10} of diphtheria antitoxin titre before and after a booster dose of toxoid. The primary immunization had been given in two doses with an interval of one year. (In one case a second blood sample could not be obtained.) See notes to Fig. 1.

within ten days of the booster inoculations. This rise was in no way dependent on the titre prior to the booster dose. The difference between children with one and those with two initial injections is not statistically significant.

Variance analysis according to the same method showed the probability of a chance difference to lie between 0.05 and 0.2.

Discussion

The results presented above clearly show that immunization with one or two injections of the toxoid preparation used is not adequate to ensure the persistence of effective protection—as measured by the antitoxin titre of the serum—after the lapse of 5 years. A single injection, however, is sufficient to provide for that period a basal immunity consisting of a state of heightened reactivity, so that the production of antibodies in response to a booster dose will have the character of a "secondary response". The possibility of obtaining high antitoxin titres within ten days implies a significant epidemiological value for basal immunity, even after so long a period as five years. A population which possesses this basal immunity can, should an epidemic threaten, receive considerably reinforced protection within a sufficiently short time. If no such basal immunity exists, the epidemiological value of inoculation is limited by the very slow pace of antitoxin production.

Basal immunization in two doses gives no certain improvement of the response to the booster dose. Whether or not a difference may be apparent after a longer period—say 10 years—cannot yet be judged.

Whether the antitoxin titre obtained by the procedure outlined here ensures complete protection can only be decided by extensive clinico-epidemiological studies. These were not included in the purpose of the present investigation and, indeed, are not possible with the present low diphtheria incidence in Sweden. IPSEN showed that the antitoxin titre might be high in the early course of clinical diphtheria, but in his cases the rise might have occurred after infection. Whether or not there is an anti-infectious component in immunity against diphtheria is as yet uncertain. No definite evidence has been produced of its clinical or experimental significance (SHEIBEL, O'MEARA, KÅSS). We must therefore continue to regard a high antitoxin titre as the best, and indeed the only, experimental criterion of immunity against diphtheria. The titres obtained after the booster injection in this study were in no case less than 0.5 I.U. They were thus considerably in excess of the requirements postulated for the immunity corresponding to the previously accepted "Schick level", which was held to be reached at about 1/30 I.U./ml, and of the higher level we ourselves considered desirable.

Summary

Thirty-one children were given a booster dose of adsorbed diphtheria toxoid five years after the primary inoculations which, after this period, had in many cases left no titrable antitoxin. The booster dose produced, within ten days, a sharp rise in the antitoxin titre in all cases. The basal immunity remaining after the primary inoculation is considered to be of great practical importance in epidemiology.

Immunité basale active et ses applications à l'épidémiologie. II. Immunité basale et réponse secondaire au cours de la prophylaxie de la diphtérie.

31 enfants reçurent une dose de toxoïde diphtérique adsorbée, 5 ans après l'inoculation primitive, laquelle après ce laps de temps ne laisse derrière elle qu'un taux d'antitoxine indosable. La dose produisit, après 10 jours, une ascension aiguë du titre des antitoxines dans tous les cas. L'immunité basale persistant après l'innoculation primaire doit, par conséquent, être considérée comme très importante d'un point de vue épidémiologique.

Aktive Basisimmunität und ihre Bedeutung für die Epidemiologie. II. Basisimmunität und Sekundärreaktion bei der Diphtherieprophylaxe.

31 Kindern wurde 5 Jahre nach der Erstimpfung (bzw. den Erstimpfungen) eine wiederholte Dosis adsorbierten Diphtherietoxoids gegeben. Nach diesem Zeitraum war in vielen Fällen kein titrables Antitoxin mehr vorhanden. Die wiederholte Dosis rief innerhalb von zehn Tagen in allen Fällen einen raschen Anstieg des Antitoxintiters hervor. Der nach der Erstimpfung resultierenden Basisimmunität wird eine grosse praktische Bedeutung für die Epidemiologie zugesprochen.

Inmunidad básica activa y su aplicación a la epidemiología. II. Inmunidad básica y respuesta secundaria en la profilaxis de la difteria.

Se administró a 31 niños una dosis fomentadora de toxoide diftérico adsorbido cinco años después de la primera inoculación, los cuales, después de este período, poseían una antitoxina no titrable. La dosis fomentadora produjo, en el curso de 10 días, un aumento intenso en el título de la antitoxina en todos los casos. La inmunidad básica que queda después de la primera inoculación, se considera que tiene una gran importancia práctica para la epidemiología.

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Received 28.2.1953.

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Acta Pædiatrica **42**: 548—569. Nov. 1953

PROGRESS IN PEDIATRICS

Acute Complications in Juvenile Diabetes Mellitus

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The prognosis in juvenile diabetes mellitus has improved steadily, and late vascular complications have not as yet caused any rise in the *mortality* rate. The general death rate from diabetes in persons below the age of 25 years is at present approximately four times lower than 30 years ago, being 3—4 per 100 000 in 1920 and 1 per 100 000 in 1950 (JOSLIN *et al.*). The mortality rate among juvenile diabetics has fallen concurrently from about 60 per cent to about 10 per cent or even lower (DUBLIN, DUBLIN & MARKS, JOSLIN *et al.*, LARSSON *et al.*, and others). The expectation of life for a 10-year-old diabetic may now be calculated to be approximately 45 years as compared to 3 years in 1920 (DUBLIN). The factors which have contributed to this development are improved insulin preparations and increased experience of their most adequate use, improvements in dietetic treatment, increased knowledge of the nature and treatment of diabetic acidosis and the introduction of antibiotics. In a survey from the Boston Clinic of the causes of death among 12 281 diabetics of all ages (Table 1) the mortality rate from diabetic coma is seen to have fallen from 41.5 per cent in 1914—1922 to 1.8 per cent in 1944—1951, the corresponding figures for acute infections being 12.7 and 6.6 per cent (JOSLIN *et al.*). In a Swedish series of 247 diabetic children given a normal diet (LARSSON *et al.*) the mortality in 1930—1950 was 1.6 per cent from diabetic coma and 2.4 per cent from acute infections.

The *morbidity* in coma and infections has not, however, decreased to the same extent. No investigation of the incidence of acute complications among diabetic patients given a normal diet of the type used in Sweden appears, however, to have been made. This fact motivated the present study. A survey was made of the diabetic in-patients at Crown Princess Lovisa's Children's Hospital during the 10-year period 1942—1952, with particular reference to the immediate cause of their admission.

During this period 218 patients with diabetes (121 boys and 97 girls) were admitted to the hospital on 500 occasions (Fig. 1). Of these patients, 96 (44

TABLE 1

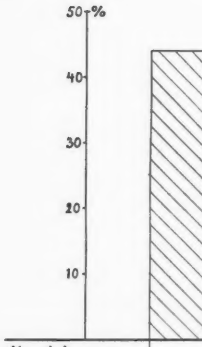
Causes of Death of 12 281 Diabetics.

(Statistical Bureau of the Metropolitan Life Insurance Company, according to JOSLIN *et al* (3).)

	1898–1914		1914–1922		1922–1936		1937–1943		1944–1945	
	No.	%	No.	%	No.	%	No.	%	No.	%
Diabetic coma	208	63.8	347	41.5	343	8.3	102	2.9	63	1.8
Cardio-renal-vascular disease	57	17.5	206	24.6	2251	54.4	2286	65.7	2478	70.8
Infections (acute)	24	7.4	106	12.7	563	13.6	363	10.4	230	6.6
Tuberculosis	16	4.9	41	4.9	170	4.1	79	2.3	66	1.9
Other causes	21	6.4	136	16.3	811	19.6	652	18.7	662	18.9
Total	326	100.0	836	100.0	4138	100.0	3482	100.0	3499	100.0

per cent) were admitted once, whereas the remaining 122 were admitted on more than one occasion. The distribution of these 500 periods of hospitalization according to the respective illnesses is shown in Table 2. Slightly more than one-fourth of the material (142/500 = 28.4 per cent) consisted of patients with fresh diabetes. The rest of the series consisted of patients with previously diagnosed and treated diabetes. They comprised both patients who had attended our Diabetic Out-Patients' Department since the onset of the disease and those who had attended some other hospital and who had been referred to our hospital by their own physician, or were admitted to it for some other reason. Of the fresh cases, 24 (16.9 per cent) were in diabetic coma and the remaining 118 (83.1 per cent) were uncomplicated cases. Approximately half (48.8 per cent) of the old cases suffered from acute complications; 34 (9.5 per cent) of these patients were in coma. Eight of these 34 patients had never been under our control before the onset of coma. Altogether 49 patients were admitted to the hospital for coma on 58 occasions. This corresponds to an incidence of 11.6 per cent during the 10-year period in question.

The largest group (146 cases = 40.8 per cent) consisted of patients admitted for readjustment because of considerably increased insulin requirement, a labile sugar balance, or excessively high glycosuria, in some cases accompanied by acetonuria. Late complications necessitated hospitalization in 2.0 per cent of the cases; only 2 of these patients suffered from vascular disease. The reason for this low figure is that when late vascular complications develop, the patients are as a rule over-age for admission to a children's hospital.



No. of times in hospital	1	2	3	4	>4	TOTAL
No. of patients	96	53	31	16	22	218
No of hospitalizations	96	106	93	64	141	500

Fig. 1. Frequency of hospitalization.

Illnesses other than diabetes were present in 8.4 per cent; 4 of these patients had epilepsy.[1] The incidence of epilepsy in a comparable series of non-diabetic children is not known, but the incidence in the present series is presumably higher than in non-diabetics. WHITE also found a rising incidence of epilepsy in her series after 1936; she attributed this to the ability of depot insulins to reveal latent convulsive disorders. Patients with a tendency to insulin hypoglycaemia are also stated to show electroencephalographic abnormalities (JOSLIN *et al.*).

Mortality. Nine patients in the whole series died, 8 of them of diabetic coma and 1 of a cerebral abscess.[2] The total mortality rate was thus 4.1 per cent, of which 3.7 per cent was due to coma. In a larger series from this clinic, of which a report was given earlier (LARSSON *et al.*) with regard to the effect of normal diet on the incidence of late vascular complications, the mortality from diabetic coma was — as already mentioned — lower, *i.e.*, 1.6 per cent. The difference is due, among other matters, to the fact that the deaths from coma in patients with fresh, previously undiagnosed and untreated diabetes were not included in the earlier series, as those patients who died at the onset of the disease obviously could not be included in an analysis of the late effects of a certain kind of treatment.

[1] After compiling the present series, an additional diabetic patient with epilepsy has been treated at the hospital.

[2] After the present investigation was concluded, one patient died of otogenic pneumococcal meningitis.

TABLE 2

Causes of 500 Hospitalizations of 218 Patients, 1942—1952.

	No.	Per cent		Deaths
Fresh cases				
Coma present	24	16.9		5
Coma absent				
with acetonuria 96				
no » 22	118	83.1		
Total	142	100.0		5
Old cases				
Coma present	34	9.5	48.8	3
Hypoglycaemia (39 patients)	48	13.4		
Infections (63 patients), no coma	93	25.9		
Admissions for readjustment				
with acetonuria 49				
no » 97	146	40.8		
Late complications				
Nephropathy 1				
Eye lesions 1				
Retardation of growth 4				
Hepatomegaly 1	7	2.0	51.2	
Other diseases				
Epilepsy (4 patients) 7				
Behaviour problems 5				
Asthma (2 patients) 4				
Miscellaneous 14	30	8.4		1
Total	358	100.0		4

Hypoglycaemia is seldom severe or troublesome when a normal diet is given. The majority of such cases do not require hospital care. However, in 48 cases in the present series, hospitalization was necessary. In 35 cases it was so severe that unconsciousness was present on admission, in some cases with convulsions. Rapid recovery took place in every instance after the intravenous or oral administration of glucose.

Infectious diseases were present on 117 occasions (Table 3). Diabetic coma occurred in 24 of these. The remaining 93 cases had no acidotic symptoms and were all unaffected (with the exception of possible fever caused by the infection), fully conscious and able to take fluid by mouth. No severe or threatening infection was present in this group.[1] Mild infections of the respira-

[1] See note 2 page 550.

TABLE 3

Type of Infection in 83 Diabetic Patients, Admitted to Hospital on 117 Occasions.

Type of infection	No. of admissions				Total
	Coma present (20 patients)		Coma absent (63 patients)		
	Fresh cases	Old cases	With acetonuria	Without acetonuria	
Upper respiratory tract infections .	5	9	26	13	53
Pneumonia	—	2	5	1	8
Gastro-intestinal infections	1	2	11	7	21
Hepatitis	—	—	2	3	5
Urinary tract infections	—	1	2	3	6
Tuberculosis (1 patient)	—	—	—	4	4
Miscellaneous (e.g. otitis, skin inf., inf. teeth)	1	3	8	8	20
Total	7	17	54	39	117

tory or gastro-intestinal tract predominated. In most of these 93 cases hospitalization was on the grounds of acetonuria accompanying the infection. This generally required increased doses of insulin for a few days, usually in the form of one or several extra doses of regular insulin.

Diabetic coma

This group is of greatest interest. It is difficult to give a satisfactory definition of coma that will include all cases of diabetic acidosis. If it is applied only to wholly unconscious patients with maximal acidosis, numerous slighter but unquestionably acidotic cases will be excluded (ROOT). This is not feasible in a discussion of the clinical aspects and treatment of coma. To follow ROOT's suggestion and base the definition on the carbon dioxide combining power of the blood plasma — all cases with a CO_2 value of 20 volumes per cent (9 millieq./lit.) or less being denoted as diabetic coma — was not possible in the present series, since the alkali reserve was unfortunately not determined in every case. Nor does such a definition include the rare, paradoxic cases of coma described by BOULIN *et al.* In such cases the patient has a normal, or even increased, CO_2 combining power as a result of extreme loss of chlorides due to vomiting or some other cause. Such a case was found in the present series: the patient was a 17-year-old girl with an infection of the urinary tract, vomiting and secondary diabetic coma.

In the present series, diabetic coma was considered to be present in all those patients who exhibited some degree of disturbance in consciousness, from slight drowsiness to deep unconsciousness, accompanied by clinical or chemical signs of acidosis in the blood or urine or both. Even if this definition is theoretically unsatisfactory, it has been found to suffice for clinical and practical purposes.

Essential differences in several respects were found in the present series between coma occurring in earlier undiagnosed, untreated cases of diabetes and in patients with known diabetes under insulin treatment, as the following analysis will show.

The *degree of severity* varied. A larger number of severe cases were found among the 24 patients with fresh diabetes than in the other group. Thus, 18 of the former patients were entirely unconscious, whereas 6 were only drowsy. Fluids could be given by mouth in 7 cases. 'Kussmaul breathing' was present in every case. Among the 34 cases with previously known diabetes, 23 patients were somnolent and 11 were only drowsy. Fluids could be given orally in all these 11 cases. No definite Kussmaul breathing could be observed in 5 patients in this group.

The *age distribution* is shown in Fig. 2. A comparison between the patients with fresh diabetes with and without coma shows a preponderance of younger children in the former category. The risk of coma in fresh diabetes is thus greater the younger the patient. The age distribution of the patients with coma among those with earlier diagnosed and treated diabetes is fairly even.

Precipitating factors. With few exceptions, no definite factor precipitating the coma could be demonstrated in *the fresh cases.* In one patient the onset took place in association with acute rheumatic fever and pancarditis, and in another it accompanied ulcerative enterocolitis. In a further 5 cases there were slight symptoms of a mild infection of the upper part of the respiratory tract. In the other patients in this group there were no signs of any other disease than diabetes. Symptoms of diabetes had been present, on an average, for 17.5 days before the first signs of coma appeared, ranging between 3 days and 6 weeks. As a comparison, it may be mentioned that in the fresh cases of diabetes without coma, symptoms were present, on an average, for one month in cases with acetonuria and for two months in those without acetonuria (Table 4). The history was thus considerably shorter in the patients with coma. In every instance coma could probably have been prevented if the diagnosis had been made in time. In the majority of cases, the parents were at fault; despite definite signs of illness in the child they had failed to consult a physician. In a few cases there was evident neglect.

A 6-year-old boy was allowed to lie at home unconscious for almost 10 hours before a physician was called. Another 5-year-old boy became ill

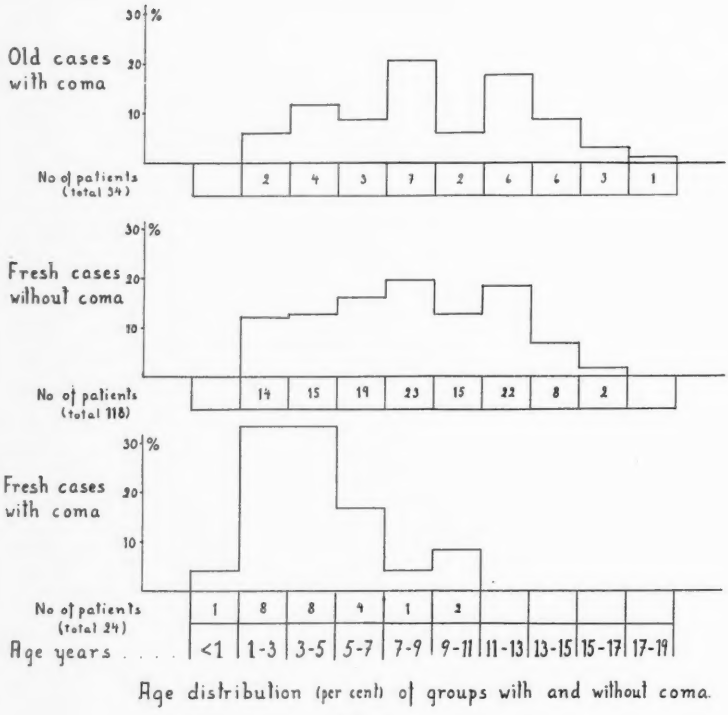


Fig. 2.

during a visit to the country. So little attention was paid to him that his parents were only sent for when he started to become unconscious. The life of neither of these patients could be saved.

Even in those cases in which a physician was sent for, the diagnosis was not always made immediately or the most suitable measures taken. In a not inconsiderable number of cases, the physician concentrated his attention on the abdominal symptoms, such as constipation, anorexia or pain, caused by the illness and failed to test the urine. A few such patients were referred to a surgical out-patients' department as uncertain abdominal cases. The diagnosis of diabetes was then either made or — as unfortunately occurred in one fatal case — the patient was sent home without a diagnosis and during the night lapsed into final unconsciousness. In other cases the physician tested the urine and even found glycosuria — at times, however, only as an "uncertain" positive test — and suggested that the patient should return in a few days for a further test. In the meantime, an acute exacerbation oc-

curred at home. Such cases emphasize the importance of immediate hospital care as soon as diabetes is suspected.

In the 34 *patients with previously known and treated diabetes*, an infectious coma-precipitating factor was found in 17 cases. Infections of the upper respiratory tract predominated. There were some cases of pneumonia, otitis media or gastro-enteritis (Table 3). Vomiting, with or without symptoms of infection, was present in 18 cases. This constitutes a further difference to the group of fresh cases, in which vomiting was uncommon. It was not always possible to determine whether the vomiting was a result of the infection or secondary to acidosis.

As among the fresh cases, several instances of severe neglect were also found in this group.

In several instances coma was preceded by carelessness or failure to give insulin. In two cases the mothers had intentionally, without consulting the hospital, ceased to give their children insulin for several weeks. When the patients finally returned to us with severe acidosis, one of them was already moribund and died two hours after admission. In another case — a neglected child of divorced parents — insulin every other day was considered to suffice, since the child's excessive hunger was attributed to insulin reactions. Actually, the doses of insulin were far too small; the patient had marked glycosuria with resulting polyphagia, and coma developed rapidly. Another patient, a 15-year-old resident in Stockholm's archipelago, refused to take the offered advantage of a flying ambulance. He made the 5-hour journey by boat instead and during it sank into a final state of unconsciousness.

These cases show *the importance of careful and continuous supervision of diabetic patients*, including detailed instructions to parents and patients with regard to the nature and treatment of the disease.

In both coma groups we have seen cases simulating appendicitis (McKITTRICK, BEARDWOOD, BERNING). These patients had abdominal pain and vomiting together with a rigid abdomen and tenderness for palpation on the right side. In three such cases the surgeon consulted urged an operation; in one of these cases a pre-operative diagnosis of peritonitis was even made. The appendix was innocent in all three cases, and no intra-abdominal explanation of the symptoms could be found at operation.

The initial *blood sugar level* on admission in the coma cases, compared with the corresponding value in the patients with fresh diabetes but no coma, is shown in Fig. 3 and Table 4. As could be expected, there was a tendency to higher values in the patients who were in coma but exceptions were found, a fact which may be of diagnostic importance. There were thus coma patients

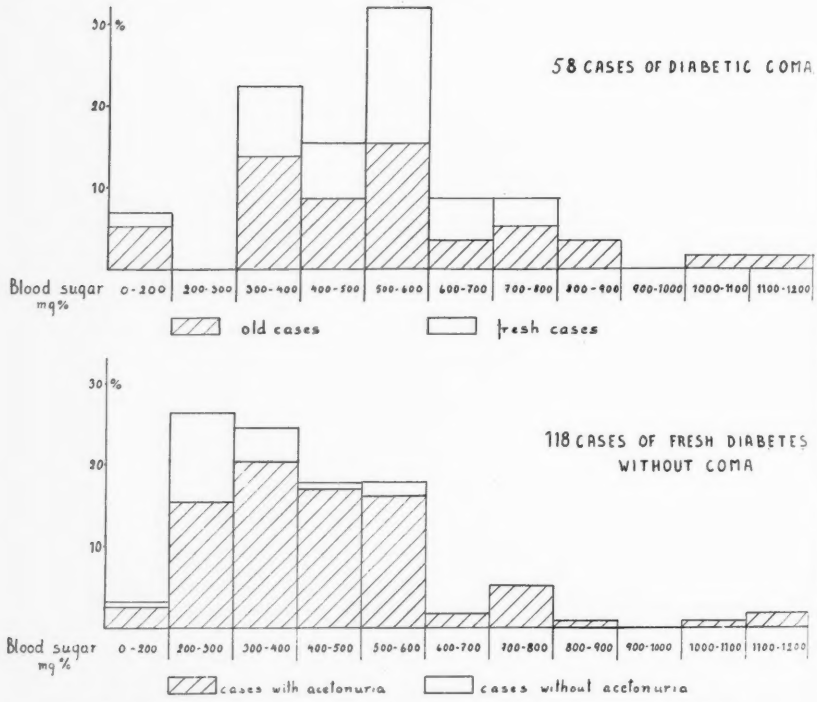


Fig. 3. Blood sugar level on admission in groups with and without coma.

in our series with a blood sugar level below 200 mg per cent; they were usually patients who had had severe, repeated vomiting before admission. But we have also seen completely unaffected patients without coma in spite of blood sugar values of 1 000—1 200 mg per cent.

Treatment. The treatment of the coma patients in the present series was not uniform. This was partly because the series dates from a period during which the principles for treatment of diabetic coma were under discussion and we wished to test the value of different procedures. It was also partly due to the fact that the fairly great variation in the degree of severity and type of the cases necessitated highly individualized treatment. During the past two to three years we have followed the principles for coma treatment that have been thoroughly discussed and substantiated by, among others, GUEST, NABARRO *et al.*, HOWARD, and HARTMANN *et al.* Briefly, this treatment consists of the following measures.

1. Continuous *supervision* of the patient and close co-operation between the physicians, nurses and the laboratory are a *sine qua non* for successful

treatment of coma. As long as the condition of the patient is critical, the physician and nurse responsible should be relieved of other work.

2. *Insulin.* We have not followed any hard and fast rules, but have used highly individualized doses. It is important not to give too small doses on the grounds of exaggerated fear of hypoglycaemia. There is no initial possibility of determining whether insulin resistance with a high insulin requirement is present or whether more moderate doses will suffice. Irreversible damage to the tissues, particularly those of the central nervous system, may, however, result from overdoses of insulin. It is therefore wise to start with a moderately large dose and then, if it is ineffective, to increase the dose rapidly. Opinions vary with regard to how often insulin should be given. In severe cases we have given it at approximately hourly intervals and consider, as does NABARRO, that there are no grounds for administration at shorter intervals which, moreover, makes it more difficult to judge the effect. As the *coma-inhibiting dose* we have considered that quantity of insulin required to eliminate all clinical and chemical signs of acidosis (Table 4). In practice, this is equivalent to the quantity of insulin given when the patient has become lucid and orientated, is able to take nourishment by mouth and the urine is free from ketone bodies.

In the fresh cases of diabetes, the mean coma-inhibiting dose was 510.4 units (corresponding to 28.8 units per kg of body weight); the corresponding figure for the old cases of diabetes was 228.4 units (corresponding to 8.2 units per kg of body weight). The distribution is, however, uneven owing to the presence of a few insulin-resistant cases. If the median is calculated for the two groups, the coma-inhibiting dose is 108 and 120 units, respectively (corresponding to 5.7 and 5.0 units per kg of body weight, respectively).

3. *Administration of fluids and electrolytes.* Intravenous administration was necessary for effective replacement in the majority of our cases. The quantity and the rate of infusion varied in the individual case. During the first 24 hours, the quantity did not, however, exceed 10—15 per cent of the body weight. The rate of infusion was most rapid during the first hours of treatment. Initially, *glucose* is contra-indicated when the blood sugar is still at an excessively high level. It increases diuresis and may therefore cause continued dehydration and loss of electrolytes (FRANKS *et al.*, LEE *et al.*, GUEST). When the effect of insulin has become evident and the blood sugar approaches normal, glucose is necessary in order for the organism to utilize the insulin and restore its depleted supply of carbohydrates. This usually occurs 3—6 hours after the beginning of treatment. The opposite applies to *alkali.* At the beginning of treatment, the administration of alkali increases the effectivity of insulin, as has also been demonstrated experimentally by MACKLER *et al.* Early administration of alkali also counteracts tissue damage

TABLE 4

Duration of Symptoms, Blood Sugar Level, Insulin Dosage and Mortality in Cases of Coma.

	Fresh cases without coma		Diabetic coma	
	Without acetonuria	With acetonuria	Fresh cases	Old cases
Number of patients	22	96	24	34
Mean duration of symptoms before hospitalization (days)	59.5	33.1	17.5	—
Blood sugar, initial value (mean)	312	456	514	540
Insulin				
Coma-inhibiting dose, total (units)				
Mean			510.4	228.4
Range			20–5656	16–1000
Median			108	120
Coma-inhibiting dose, units per kg				
Mean			28.8	8.2
Range			1.0–288.6	0.5–30.0
Median			5.7	5.0
Stabilizing dose, (units)				
Total (mean)			17.9	54.6
Per kg (mean)			1.1	1.9
Mean time of unconsciousness after admission (hours)			19.1	15.7
Mortality				
Number			5	3
Per cent			20.8	8.8

caused by acidosis. As the effect of insulin increases, continued administration of alkali is, however, unsuitable since at this stage it may prevent normal cellular repair and lead to alkalosis. Nor should the primary administration of alkali aim at complete normalization of the plasma carbon dioxide combining power. It is suitable to give, as GUEST has suggested, sufficient alkali to raise the plasma bicarbonate index to approximately 15 millieq./litre (0.058 g of $NaHCO_3$ per kg of b.w. raises the CO_2 content of the plasma by 1 millieq./litre).

Sodium and *chloride* are indicated to compensate for the extracellular losses during the first stage of treatment. Too exclusive administration of saline or of Ringer's solution is, however, associated with a risk of overdosage, when the sodium may penetrate into the cells — particularly when the serum po-

tassium is low — and lead to disturbances in intracellular metabolism. Overdosage of chloride may maintain acidosis by displacement of bicarbonate.

The changes in the *potassium* balance of the body — and to some extent the *phosphate* balance as well — in the course of diabetic acidosis and the clinical consequences of these changes have been the object of detailed studies by HOLLER, BUTLER *et al.*, GUEST *et al.*, NADLER *et al.*, GREENMAN *et al.* and MARTIN *et al.*, among others. Briefly, these investigations have shown that, before treatment is given, potassium and phosphate pour out of the cells — presumably owing to metabolic cellular damage — so that hyperpotassaemia and hyperphosphataemia occur, despite the fact that there is actually a potassium deficit in the body. Therefore, initial administration of potassium implies a risk of potassium intoxication. When, as a result of the insulin given, the metabolism starts to return to normal with falling blood sugar, improved utilization of glucose and liver glycogenesis, the cells start to assimilate potassium and phosphate. Unless sufficient quantities of these electrolytes are then available in the plasma, a severe hypopotassaemic condition may arise. Numerous obscure deaths from diabetic coma at this stage may presumably be explained on the grounds of potassium deficiency. Other factors such as the degree of dehydration, the excretion of potassium in the urine and the nutritional state of the patient, are also of importance for the potassium balance of the body.

In the present series it was not possible to make systematic determinations of the serum potassium, but ECGs were recorded regularly. A directly recording apparatus proved to be useful for this purpose. None of the electrocardiographic changes described by HOLLER, MARTIN *et al.*, BELLET *et al.* and MERRILL, among others, as typical of potassium deficiency were observed in any of the patients in this series.

Butler's solution was used to supply potassium. From a stock solution[1] 5 ml were added to 100 ml of 5—10 % glucose solution. As soon as the patients were able to take fluids by mouth, food rich in potassium (*e.g.* orange juice and milk) were given. The administration of potassium is contra-indicated in the presence of anuria.

To sum up, the following fluids and electrolytes were given intravenously in severe acidosis. During the first 3—6 hours, equal parts of Ringer's solution and 1.3 per cent solution of bicarbonate. Thereafter, one of the following solutions was used: (i) Ringer's solution with (instead of bicarbonate) 5—10 per cent glucose in equal parts; (ii) Ringer's solution with 5—10 per cent glucose in a proportion of 1 : 2; (iii) 5—10 per cent glucose alone (in patients with rapidly falling blood sugar). Butler's solution was added to the glucose solution as indicated above. The composition of the solutions most commonly used is shown in Fig. 4.

[1] Natr. lact. 4.4 g, NaCl 1.2 g, KCl 2.0 g, K_2HPO_4 1.0 g, Aq. steril. 100 g.

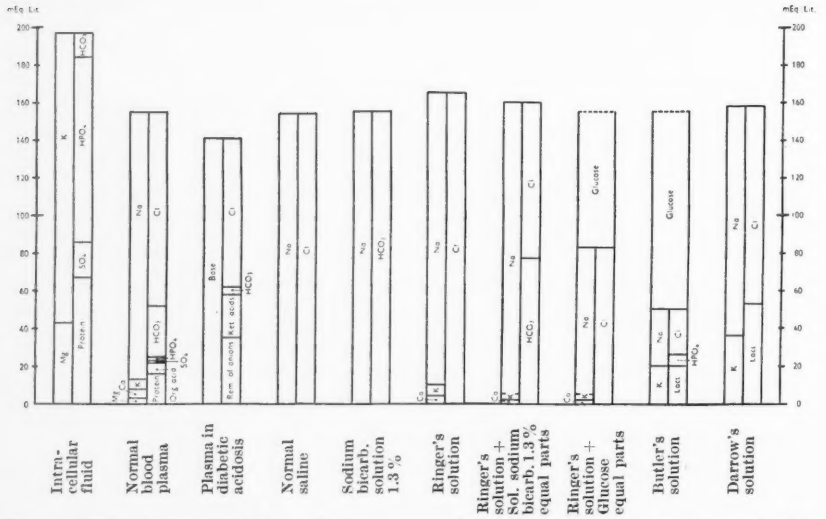


Fig. 4. Electrolyte composition of most commonly used repair solutions compared with the electrolyte composition of normal intracellular fluid, normal blood plasma, and blood plasma in diabetic acidosis (partly after GAMBLE (42)).

We have tried *thiamine pyrophosphate* or cocarboxylase in a few cases; opinions about its usefulness in diabetic coma appear to differ (MARKEES *et al.*, BOULIN *et al.*, GUEST, ROOT) and our own experience is as yet too slight to permit a definite evaluation. There are nevertheless theoretical grounds for further trial. Other factors in the vitamin B complex are also indicated in the treatment of acidosis.

The treatment has naturally also comprised general measures, such as circulatory stimulation, the administration of antibiotics and blood transfusions.

Deaths. Of the 8 patients who died, 5 belonged to the group of fresh diabetes and 3 to the old cases. The mortality was thus 20.8 per cent in the former group and 8.8 per cent in the latter; the total mortality in both groups amounted to 13.8 per cent. As far as I am aware, the difference between the degree of severity and the mortality from coma in fresh, untreated cases and in cases already under insulin treatment has not been pointed out previously. A statement is, however, found in the work of DILLON and DYER with regard to how many of their patients suffering from coma were previously undiagnosed cases. The authors did not state the mortality in this group nor discuss it in particular, but it may be calculated from their tables that the mortality in a group of 31 cases of uncomplicated coma in patients with hitherto unknown diabetes was 51.6 per cent. In a comparable group of 98 cases of earlier known and treated diabetes, the corresponding figure was 16.3 per cent.

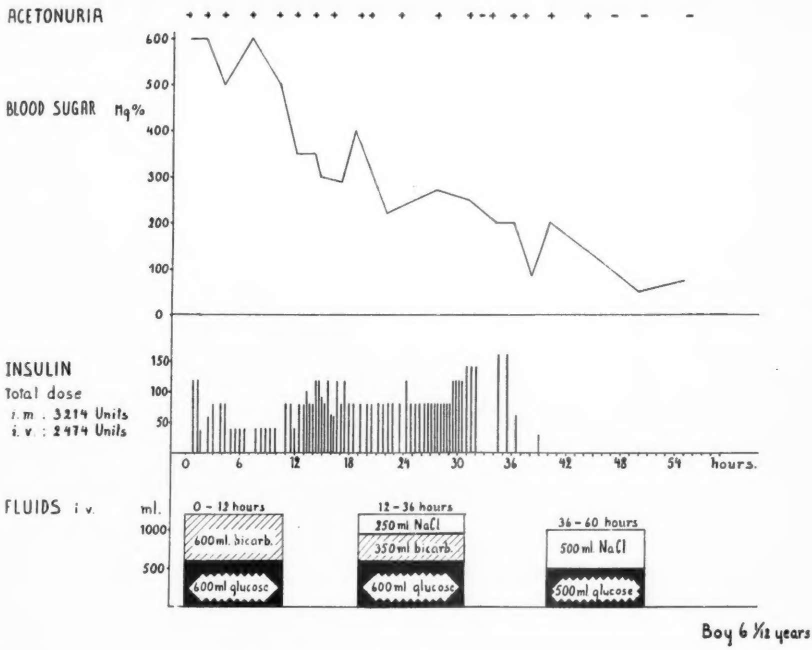


Fig. 5.

In the present series, two of the patients had normal blood sugar, a normal bicarbonate value and acetone-free urine before death. Autopsy disclosed ulcerative enterocolitis in one case and diffuse, purulent bronchitis in the other; in all probability these infections contributed to the fatal outcome. Two other patients were in an extremely neglected and poor condition on admission and died after less than six hours in hospital. If these four cases are excluded, the mortality in the coma group is 7.4 per cent. It should be possible to decrease the mortality still further by means of improved prophylaxis and therapy.

Temporary *insulin resistance* was present in three patients; the course is shown in Figs. 5, 6, and 7. The first (Fig. 5) was a 6-year-old boy with a 4-weeks' history of diabetes; he showed no signs of infection when he was admitted to hospital with marked systemic disturbances, deeply somnolent, shocked, dehydrated and acidotic. With the help of altogether 5 688 units of regular insulin (289 units per kg of body weight) and intensive fluid and electrolyte therapy, the patient was lucid and free from all signs of acidosis after about 36 hours. His diabetes could subsequently be kept under control

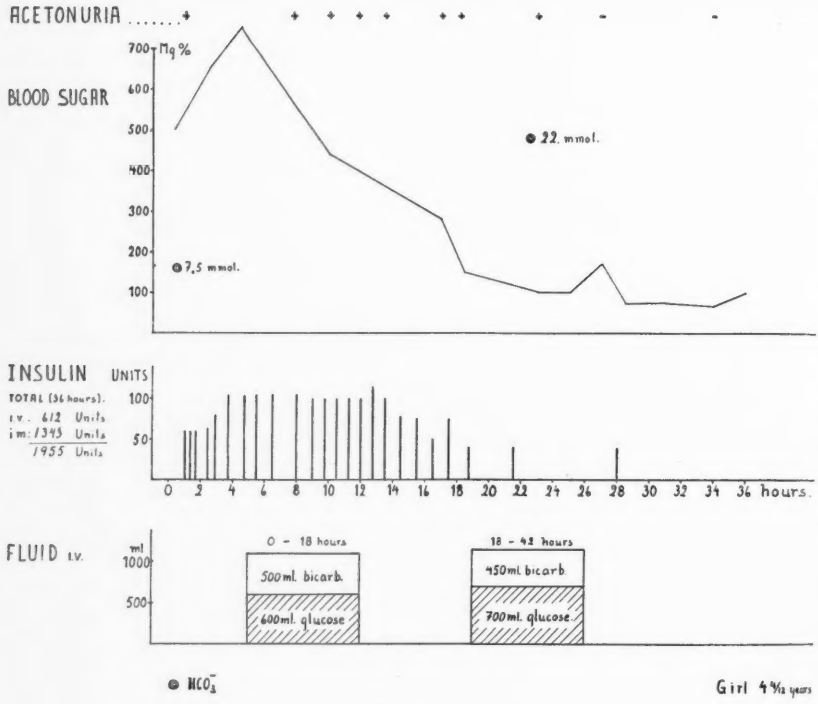


Fig. 6.

with 36 units of protamine insulin daily. Fig. 6 shows a similar case; the patient was a 4-year-old girl with diabetic symptoms for one week before admission. In this case, the coma-inhibiting dose was 1 955 units of regular insulin (130 units per kg of body weight); the final stabilizing dose was only 16 units of protamine insulin daily.

Fig. 7 shows the course in a 14-month-old girl with earlier diagnosed diabetes. For 3—4 weeks she was relatively resistant to insulin but no definite cause for the resistance could be established. During this time her insulin requirement was approximately 350 units per day, corresponding to 40 units per kg of body weight. Contrary to the two previous patients, she was fairly unaffected and never comatose during the insulin-resistant period, despite extremely labile blood sugar and moderate acetonuria.

Similar cases with transient resistance to insulin, with or without coma, have been described earlier by WIENER, MARTIN *et al.* HART *et al.*, WAYBURN *et al.*, GOLDNER *et al.*, LOWELL, MCGAVACK *et al.*, FELDER, SHEPPARD, and

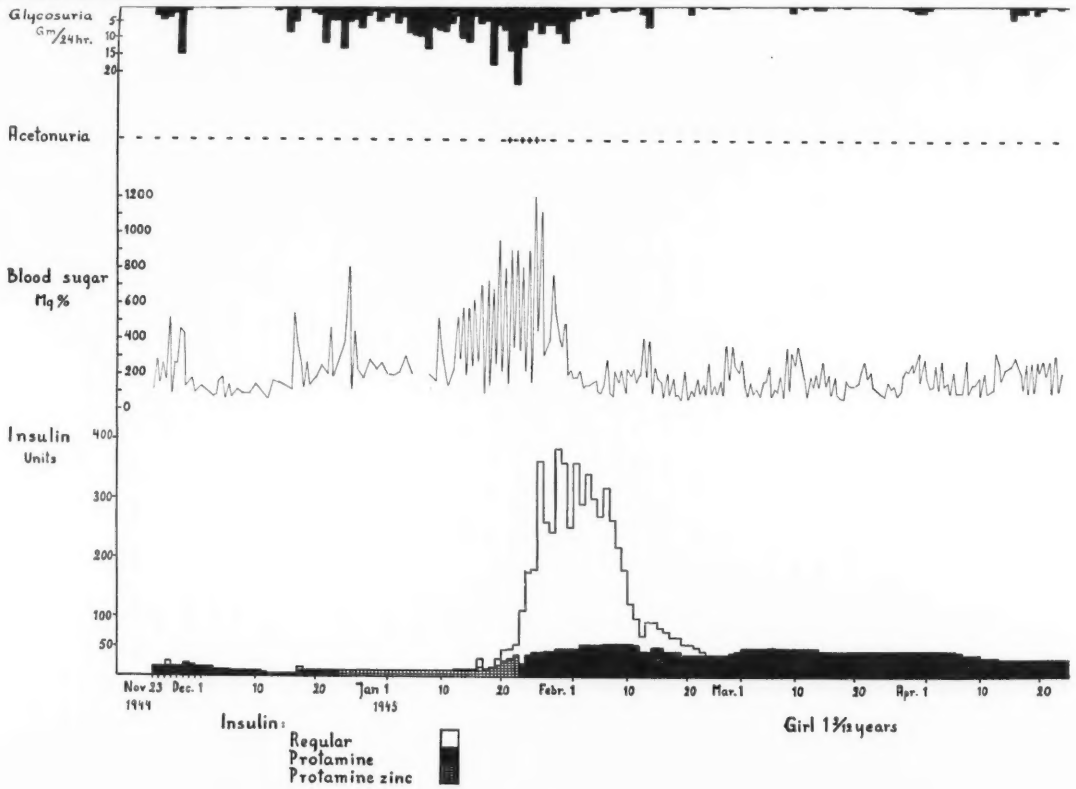

Glycosuria
Gm/24hr.
5
10
15
20
Acetonuria
Blood sugar
Mg %
1200
1000
800
600
400
200
0
Insulin
Units
400
300
200
100
50
Nov 23
1944
Dec. 1
10
20
Jan 1
1945
10
20
Febr. 1
10
20
Mar. 1
10
20
Apr. 1
10
20
Insulin:
Regular
Protamine
Protamine zinc
Girl 1 3/12 years

Fig. 7.

CRAMPTON *et al.*, among others. Various theories have been advanced as an explanation of such resistance to insulin; for example, liver damage, an excess of insulin-inhibiting factors or insulin allergy. In the majority of such cases there is, however, no definite known cause in the present state of our knowledge.

Summary

1. During the 10-year-period 1942—1952, 218 diabetic patients were hospitalized on altogether 500 occasions at the Medical Department of Crown Princess Lovisa's Children's Hospital in Stockholm. Ninety-six (44.0 per cent) were admitted on one occasion only and the remainder on more than one occasion. Fresh, previously untreated diabetes was present on 142 occasions (28.4 per cent). The rest of the series consisted of patients suffering from previously diagnosed and treated diabetes. Diabetic coma occurred 24 times in the former group and 34 times in the latter. The total coma incidence in the whole series amounted to 11.6 per cent. The mortality was 4.1 per cent (9 patients), of which 3.7 per cent was from diabetic coma.

2. Hypoglycaemia necessitated hospitalization on 48 occasions (13.4 per cent) in the diabetic patients treated with insulin. Acute infections without coma were present on 93 occasions and in connexion with coma on 24 occasions (Tables 2—3).

3. In the 58 instances of diabetic coma, essential differences were found in a comparison between the 24 cases in the fresh, previously untreated diabetics and the 34 cases in the old insulin-treated patients. In the former group there was a larger number of severe cases and the mean total dose of insulin required to inhibit the coma was larger due to the presence of insulin-resistant cases. The final stabilizing dose was, on the other hand, considerably lower in this group (Table 4). The mortality was higher among the coma cases in the previously untreated diabetics than among the coma cases in insulin-treated patients. The deaths amounted to 5 (20.8 per cent) in the former group and 3 (8.8 per cent) in the latter. The factors precipitating coma in the respective groups are discussed. Infectious factors were found to be more common in insulin-treated coma patients than in those with fresh untreated diabetes and coma.

4. A comparison of the age distribution among the fresh cases of diabetes with and without coma showed a predominance of the younger age groups in the patients with coma (Fig. 2). Symptoms of diabetes before hospitalization had been present in the cases with fresh diabetes and coma for approximately half the time (mean duration 17.5 days) of that in the patients with fresh diabetes without coma but with acetonuria (mean duration 33.1 days). In the fresh cases with neither coma nor acetonuria, the duration was still longer (mean 59.5 days).

5. The mean initial blood sugar level was higher in the fresh cases with coma than in the fresh cases without coma. Exceptions were noted: a few patients with coma and a blood sugar level below 200 mg per cent, and a few cases without coma and a blood sugar level above 1 000 mg per cent (Fig. 3).

6. The most important principles for the treatment of diabetic coma are discussed, *i.e.*, individualized doses of insulin, administration of fluids up to maximally 10—15 per cent of the body weight per 24 hours, a moderate supply of alkali during the first 3—6 hours, followed by glucose in 5—10 per cent solution, also containing sodium, chloride, lactate, potassium and phosphate (Butler's solution); Fig. 4.

7. Three cases of temporary insulin resistance are described, Figs. 5—7. Two cases occurred in association with diabetic coma; the third patient showed no signs of coma.

Complications aigues du diabète sucré chez l'enfant.

Entre les années 1942 et 1952, soit 10 années, 218 malades atteints de diabète furent hospitalisés au total 500 fois au service de médecine du Kronprinsessan Lovisas Barnsjukhus de Stockholm. 96 de ceux-ci (44.0 %) ne furent hospitalisés qu'une fois, les autres à plusieurs occasions. 142 cas concernent des diabètes «frais» non traités auparavant (28.4 %) tandis que chez les autres la maladie était déjà diagnostiquée et traitée. Le coma fut rencontré 24 fois dans le premier groupe contre 34 dans le second. Le pourcentage total de comas est de 11.6 %. La mortalité est de 4.1 % (9 malades) parmi lesquels 3.7 % comas.

L'hypoglycémie nécessita l'hospitalisation 48 fois (13.4 %) chez les malades soumis à l'insulinothérapie. Les infections aigues sans signes de coma furent rencontrées 93 fois. Elles allaient de pair avec un coma 24 fois.

Parmi les 58 cas de coma diabétique, d'essentielles différences furent constatées entre le diabète frais, non traité avant et les malades déjà soumis à l'insuline. Dans le premier groupe (24 cas), on trouve un plus grand nombre de cas sévères et la dose totale d'insuline nécessaire à la disparition du coma était plus grande, due à la présence de cas d'insulinorésistance. La dose terminale capable de stabiliser ces cas s'est montrée par contre plus basse dans ce groupe que dans l'autre. Mais la mortalité est plus importante parmi ces comas survenant chez les sujets neufs que chez ceux déjà soumis à l'insulinothérapie, 5 morts (20.8 %) dans le premier groupe contre 3 (8.8 %) dans le second. L'auteur discute les facteurs capables de précipiter un coma dans les 2 groupes. L'infection se montre plus fréquente au cours du coma des sujets en cours de traitement que du coma des sujets non préalablement traités.

Au cours du diabète frais, non traité, le coma se montra plus fréquent aux âges inférieurs que dans les groupes plus âgés. La durée des symptomes de diabète avant l'hospitalisation était parmi ceux qui arrivèrent en coma approximativement la moitié (durée moyenne: 17.5 jours) de celle chez les malades non traités avant, sans coma mais avec acétonurie (durée moyenne: 33.1 jours). Parmi les cas de diabète frais mais sans coma ni acétonurie, cette durée fut encore plus longue: 59,5 jours.

Le taux d'élévation du sucre sanguin est plus haut en cas de coma parmi les diabétiques «frais». Des exceptions furent cependant notées: un petit nombre de comas avec une glycémie à 200 mg % et d'autres sans coma malgré un taux de 1000 mg %.

L'auteur discute ensuite les principes les plus importants du traitement du coma diabétique, c'est-à-dire: doses individuelles d'insuline, administration de liquides jusqu'à un maximum de 10 à 15 % du poids corporel par 24 heures, un apport modéré d'alcalins pendant les 3—6 premières heures, suivi d'administration de glucose en solution à 5—10 % contenant de plus du potassium et de phosphate (solution de Butler).

L'auteur décrit 3 cas de résistance temporaire à l'insuline, deux associés à un coma, l'autre non.

Akute Komplikationen beim juvenilen Diabetes mellitus.

Während der Zehnjahresperiode 1942—52 wurden 218 diabetische Patienten insgesamt aus 500 Anlässen in die Innere Abteilung des Kronprinzessin-Lovisa's-Kinderhospitals zu Stockholm aufgenommen. 96 (44 %) wurden nur einmal und die restli-

chen aus mehr als einem Anlass aufgenommen. Frischer, vorher unbehandelter Diabetes lag in 142 Fällen (28,4 %) vor. Bei den Übrigen handelte es sich um früher diagnostizierten und behandelten Diabetes. Ein diabetisches Koma trat 24 mal in der ersten und 34 mal in der letzteren Gruppe auf. Die gesamte Komahäufigkeit in allen Serien betrug 11,6 %. Die Mortalität lag bei 4,1 % (9 Patienten), wovon 3,7 % auf das diabetische Koma entfielen.

Bei den mit Insulin behandelten Patienten war 48 mal (13,4 %) die Krankenhausaufnahme wegen Hypoglykämie notwendig. Akute Infektionen ohne Koma lagen in 93 Fällen und im Zusammenhang mit einem Koma in 24 Fällen vor.

Bei den 58 Beispielen von Coma diabeticum wurden echte Unterschiede beim Vergleich der 24 frischen, vorher unbehandelten und der 34 alten, insulinbehandelten Patienten gefunden. In der ersten Gruppe war eine grössere Anzahl schwerer Fälle und die durchschnittlich zur Behebung des Komas verwendete Insulinmenge lag höher infolge des Vorliegens einiger insulinresistenter Fälle. Andererseits war die endgültige Einstellungsdosis in dieser Gruppe beträchtlich niedriger. Die Mortalität war in den Komafällen des vorher unbehandelten Diabetes grösser als beim Koma der insulinbehandelten Patienten. Die Todesfälle betrugen 5 (20,8 %) in der ersten und 3 (8,8 %) in der letzten Gruppe. Die komaauslösenden Faktoren in den entsprechenden Gruppen werden diskutiert. Infektiöse Faktoren sind bei insulinbehandelten Patienten häufiger als bei frischem unbehandeltem Diabetes.

Ein Vergleich der Altersverteilung unter den frischen Diabetesfällen mit und ohne Koma zeigt ein Überwiegen der jüngeren Altersstufen bei den Komapatienten. Diabetessymptome vor der Hospitalaufnahme waren bei der Komagruppe ungefähr halb so lange (mittlere Dauer 17,5 Tage) vorhanden als bei Patienten mit frischem Diabetes ohne Koma aber mit Acetonurie (mittlere Dauer 33,1 Tage). In den frischen Fällen ohne Koma und ohne Acetonurie war die Dauer noch länger (Mittel 59,5 Tage).

Der mittlere initiale Blutzuckerspiegel lag in den frischen Fällen mit Koma höher als in den frischen Fällen ohne Koma. Ausnahmen wurden festgestellt: einige Patienten mit Koma und einem Blutzuckerspiegel unter 200 mg%, und einige Fälle ohne Koma bei einem Blutzuckerspiegel über 1000 mg%.

Die wichtigsten Richtlinien für die Behandlung des Coma diabeticum werden diskutiert, so die individuell zu dosierende Insulinmenge, Flüssigkeitszufuhr bis zu 10—15 % des Körpergewichtes in 24 Stunden, mässige Alkalizufuhr in den ersten 3—6 Stunden; anschliessend 5—10 prozentige, Kalium und Phosphate (Butler-Lösung) enthaltende Glucose.

Drei Fälle temporärer Insulinresistenz werden beschrieben. Zwei Fälle traten im Zusammenhang mit einem diabetischen Koma auf. Der dritte Patient zeigte keine Zeichen eines Komas.

Complicaciones agudas en la diabetes mellitus juvenil.

Durante el período de los últimos 10 años, 1942—1952, 218 pacientes diabéticos fueron hospitalizados en conjunto en 500 ocasiones en el departamento médico del Hospital de la princesa Luisa, de niños, en Estocolmo. Noventa y seis (44.0 por ciento) fueron ingresados solamente en una ocasión y el resto en más de una. Diabetes reciente, sin tratar, se presentó en 142 casos (28.4 por ciento). Los otros casos sufrian de diabetes previamente diagnostizada y tratada. El coma diabético se presentó 24 veces en el primer grupo y 34 en el último. La incidencia total del coma en todas las series ascendió a un 11.6 por ciento. La mortalidad fué de 4.1 por ciento (9 pacientes), el 3.7 por ciento de los cuales por coma diabético.

Ataques de hipoglucemia necesitaron hospitalización en 48 ocasiones (13.4 por ciento) en los pacientes diabéticos tratados con insulina. Infecciones agudas sin coma se presentaron en 93 ocasiones y en conección con coma en 24 ocasiones.

En los 58 casos de coma diabético se encontraron diferencias esenciales en una comparación entre los 24 casos de diabetes reciente, sin tratar, y los 34 casos de pacientes ya tratados con insulina. En el primer grupo hubo un número mayor de casos graves y la dosis media total de insulina necesaria para inhibir el coma fué mayor debido a la presencia de varios casos resistentes a la insulina. La dosis final estabilizante fué, por otra parte, considerablemente más baja en este grupo. La mortalidad fué mayor entre los casos de coma de los diabéticos no tratados que en los casos de coma de los pacientes tratados con insulina. Los fallecimientos ascendieron a 5 (20.8 por ciento) en el primer grupo y 3 (8.8 por ciento) en el último. Son discutidos los factores que precipitaron el coma en los respectivos grupos. Se encontró que los factores infecciosos son más comunes en los pacientes con coma, tratados con insulina, que en aquellos con diabetes reciente sin tratar y coma.

Una comparación de la distribución de edad entre los casos recientes de diabetes con y sin coma mostró una predominancia del grupo más joven en los pacientes con coma. Se habian presentado síntomas diabéticos antes de la hospitalización en el grupo de coma aproximadamente en la mitad (duración media 17.5 días) de casos de los pacientes con diabetes reciente sin coma, pero con acetonuria (duración media 33.1 dias). En los casos recientes sin coma ni acetonuria, la duración fué todavía más larga (59.9 días).

En nivel inicial medio de la glucemia fué más alto en los casos recientes con coma que en los casos recientes sin coma. Se registraron excepciones: algunos pocos pacientes con coma y un nivel glucémico por debajo de 200 mg por ciento y algunos casos sin coma y una glucemia alrededor de 1 000 mg por ciento.

Se discuten los principios más importantes para el tratamiento del coma diabético, es decir dosis de insulina individualizadas, administración de líquidos hasta máximo 10—15 por ciento del peso del cuerpo por 24 horas, un suplemento moderado de alcalinos durante las primeras 3—6 horas, seguido de glucosa en una solución al 5—10 por ciento, conteniendo también potasio y fosfato (solución de Butler).

Se describen tres casos de resistencia temporal a la insulina. Dos casos ocurrieron con asociación de un coma diabético, el tercer paciente no mostró ningun signo de coma.

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Received 9.12. 1952.

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Acta Pædiatrica **42**: 570—575. Nov. 1953

CASE REPORT

Essential Hypertension in a 12 Year Old Girl Treated with Hexamethonium Compounds

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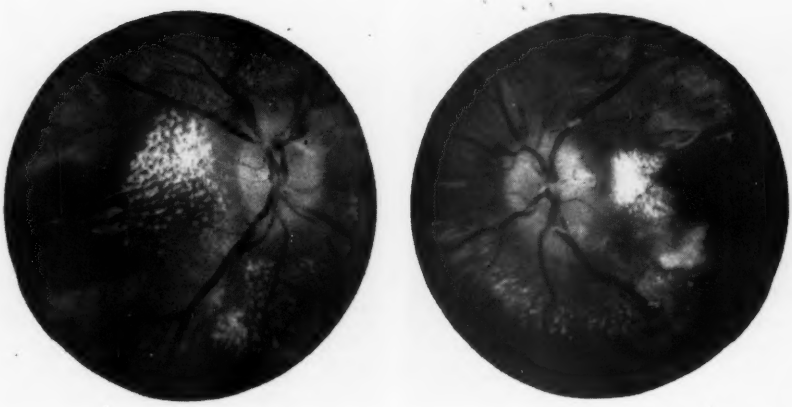
Hypertension in childhood is relatively rare. Of late, cases which have been operated upon or have come to autopsy with the diagnosis of essential hypertension, have proved to be due to a phaeochromocytoma (SMITHWICK). An exact diagnosis is of great importance in view of the therapeutic consequences. In a case of a phaeochromocytoma the tumor should be removed, while in essential hypertension medical treatment is indicated (ROSENHEIM). In view of the importance of an exact diagnosis and in connection with our experience of the administration of hexamethonium compounds the following observation is reported.

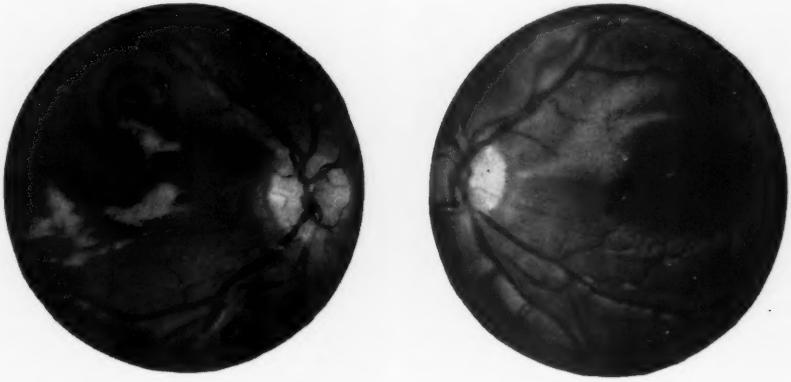
C. B., an Indonesian girl, the third child of healthy parents, was born at full term in Java in 1940, following a normal pregnancy and delivery. The development had been uneventful. After a stay in a concentration camp on Java from May 1945 till October 1946, she was severely undernourished and suffered from malaria, ascariasis and polyuria. Soon after her liberation she came to the Netherlands where a hypertension was found (190/145). This high blood pressure persisted and gave rise to increasing complaints of headache, nasal haemorrhages and visual disturbances for which she was treated in various hospitals with a low-salt and frequently a low-protein diet. On admission to the Ophthalmological Clinic of the Wilhelmina Gasthuis at Amsterdam on December 7, 1950, the vision was R. $\frac{1}{2}$ ft, L. $\frac{1}{4}$/60. The cornea, anterior chamber, iris and lens showed no abnormalities; the media were clear. In the fundi a severe retinitis albuminurica was found, the condition which was later called hypertensive neuroretinopathy: a greyish-pink papilla of the optic nerve without clear edges and many small exudates more or less arranged in the form of a star around the macula lutea. No haemorrhages were seen. The arteries were markedly constricted (generally and locally) with thickened walls. During her stay in the hospital the blood pressure was 220/160. A low-salt diet was prescribed with absolute bed-rest. The picture of the fundus of the right eye remained practically the same, that of the left eye improved slightly, while the vision of the left eye increased to 1/6. On March 15, 1951 the papillae of the optic nerves of both eyes were less hazy, but the number of white spots had increased (Fig. 1).

As a phaeochromocytoma might have been the cause of the hypertension, the child was transferred for further examination and treatment to the Children's Clinic of the Binnengasthuis (of the Municipal University of Amsterdam). On examina-



Right eye Left eye

Fig. 1. March 1951. Fundi oculi before treatment: hypertensive neuroretinopathy.



Right eye Left eye

Fig. 3. Febr. 1953. Fundi oculi during treatment: only some small scars present.

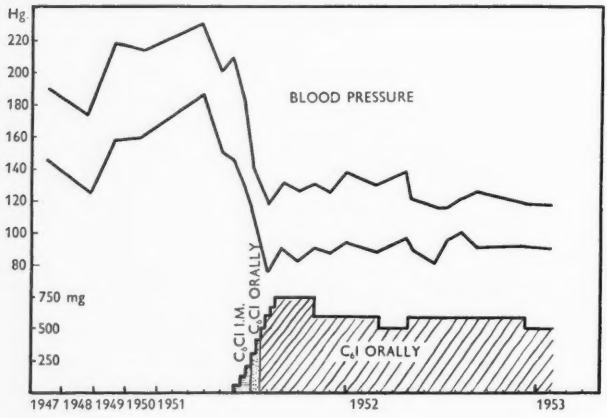


Fig. 2. Course of the disease.

tion here the blood pressure in the arms was 230/185, in the legs it was also elevated. The femoral arteries could be palpated on both sides normally. The heart was slightly enlarged to the left. The E.C.G. showed a slight left axis deviation. The blood sedimentation was 20 mm/1st hour. The only abnormality of the urine was a trace of albumen. Maximal urine concentration was 1.016. The urea clearance was 46.2 per cent. The blood picture was normal. The temperature was and always remained normal. There were no vasomotor disturbances nor excessive perspiration. There was no postural hypotension. The glucose tolerance curve was normal. The basal metabolism was +4.2 %. X-ray examination showed no abnormalities (no calcifications in the adrenal regions, normal pictures of the intravenous pyelogram). Perirenal air insufflation was not performed on account of its danger. "Prosympal," used by us instead of the non-available benzodioxane, had no influence on the blood pressure. The cold pressor test was positive: the blood pressure rose from 180/130 to 230/160 after the hand of the patient was immersed in ice water. Tetra aethyl ammonium bromide caused a small decrease of the blood pressure. The blood-adrenalin and -noradrenalin contents were normal. The 17-ketosteroids excretion in the urine was normal.

The diagnosis essential malignant hypertension was made. On May 15, 1951 we started with hexamethonium compound treatment (combined with salt-free diet). Just before treatment the condition of the fundi oculi was as follows: Round the papilla and in the region of the macula numerous small white spots were seen on both sides in a radiating pattern. No edema of retina or papilla. Some small haemorrhages, however, were present. The arteries were constricted with irregular and too broad light reflexes. A small arterio-venous compression was present.

Firstly a trial dose of 24 mg hexamethonium chloride was given intramuscularly, which resulted in a transitory decrease of the blood pressure. No side effects were seen. Thereafter we started with an intramuscular injection of 24 mg of this compound thrice daily. The dose was gradually increased. Only once the girl complained of a disturbance in accomodation. After some weeks the compound was given orally and later, when it was no longer available, it was substituted by the hexamethonium

iodide. The maximal dose given was 5 × 150 mg per day. The blood pressure values were now between 140/115 and 115/75, and no further decrease could be effected. In the meantime the general condition of the girl had greatly improved. She no longer had headaches, nasal haemorrhages or visual disturbances. On July 24, 1951 the arteries of the fundi oculi showed less constriction. On August 13, 1951 the girl was discharged from the hospital with a salt-free diet and 5 × 150 mg hexamethonium-iodide daily by mouth. During a follow-up period—already 18 months—the general condition remained good and the blood pressure could be maintained at an approximately normal level. No disagreeable symptoms from the drug were seen. The dosage was first diminished to 4 × 125 mg daily, but later it was increased to 4 × 150 mg (Fig. 2). In December 1951 the vision after correction was R. 1 and L. 3/60. In the right eye a small central scotoma for 10/25 blue and red was found. The papilla of the optic nerve was normal apart from a very slight haziness. The diameter of the arteries was normal without any arterio-venous compression. A single branch of the left inferior temporal artery had a pathologically broadened reflex; temporally of the papilla some fine spots were still present. In the left macula lutea many yellowish granules were seen. Some small chorioretinal scars were present in the periphery of both retinae. Since then the fundi have not much changed (Fig. 3, February 1953). In February 1952 there was—except for a trace of albuminuria—no abnormality of the urine or renal function. This remained the same until the last examination in February 1953. The general condition is excellent. The dosage of C_6I was in December 1952 again diminished to 4 × 125 mg daily without any unfavourable effect on the blood pressure. The weight increased during the last 12 months by 4 kg and is now 36.5 kg. The girl lives as any normal and healthy girl.

Discussion

The results of the examination of this girl made clear that she was suffering from essential hypertension grade IV according to KEITH, WAGENER and BARKER with a very bad prognosis. The differential diagnosis from phaeochromocytoma may be very difficult. In Table I the differences between the two conditions are summarized. However, each of the tests may give false positive results. The most reliable test is the benzodioxane test.

Hexamethonium compounds exert their favourable activity by a blockage of the adrenergic impulses in the ganglia causing a general peripheral vasodilatation (ARNOLD and ROSENHEIM; BURT and GRAHAM). These compounds, however, have also a paralysing effect on the parasympathetic ganglia (PATON and ZAIMIS) whereby they can give rise to disturbances of accomodation, parched mouth, constipation or abdominal distension.

As hexamethonium compounds cause a postural hypotension, it is necessary that this substance is given while the patient is in the erect position. If the blood pressure falls too much—the patient may even become unconscious—the patient must be brought into the recumbent position.

The results of the treatment with hexamethonium in our patient are striking: with a maintenance dose the blood pressure remains at an approximately normal level. The expected development of the hypertensive retinopathy to a terminal stage seems to be interrupted. The general condition of the patient improved and all complaints disappeared.

TABLE I

Differential diagnosis: essential hypertension–phaeochromocytoma.

	Essential hypertension	Phaeochromocytoma
Blood pressure	Constantly elevated	Often paroxysmal hypertension
Basal metabolism	Normal	Often increased
Glycosuria	—	Often +
Pyrexia	—	Often +
Vasomotor disturbances	—	Often +
Postural hypotension	—	Often +
Glucose tolerance test	Normal	Often like in diabetes
Adrenalin, noradrenalin	Normal	Often increased
X-ray examination	Normal	Often abnormalities
Histamin test i.v.	Bl. press. falls, or no reaction	B. p. increases
Mecholyl test	Bl. press. falls	Slight incr. or no reaction of b. p.
Tetra aethyl ammonium i.v.	Bl. press. falls	B. p. increases
Benzodioxane test	No reaction	B. p. falls
Dibenamine	No reaction	B. p. falls
Sedation test	Slight fall of b. p.	No reaction
Cold pressor test	B. p. increases	No reaction

Note at the correction

In July 1953 the dosage of C_6I was reduced to 4×100 mg daily. The general condition of the girl remained good and the bloodpressure remained at a normal level. The period of treatment lasts now 2 years and 4 months.

Summary

Description of a 12 year old girl suffering from malignant hypertension, grade IV, and treated with hexamethonium compounds with striking results. The blood pressure fell to normal values and all symptoms of the disease including the retinal changes disappeared. The period of treatment is by now twenty months. Before treatment the possibility of a phaeochromocytoma was excluded.

Hypertension artérielle chez une fille âgée de 12 ans, traitée par l'hexaméthonium.

Les auteurs rapportent l'observation d'une fillette de 12 ans atteinte d'hypertension maligne au stade IV traitée à l'hexaméthonium avec un résultat remarquable. La TA tomba à des chiffres normaux et tous les signes de la maladie, y compris les modifications du fond d'œil, disparurent. La durée du traitement fut d'environ 20 mois. Avant traitement, la possibilité d'un "phaeochromocytome" fut exclue.

Essentielle Hypertonie bei einem 12jährigen Mädchen, behandelt mit Hexamethonium-Compound.

Beschreibung eines an malignem Hochdruck (Grad IV) leidenden 12jähr. Mädchens, welches mit auffallendem Erfolg mit Hexamethonium-Compound behandelt wurde. Der Blutdruck fiel auf normale Werte ab und alle Symptome einschließ-

lich die Retinaveränderungen verschwanden. Die Behandlungsdauer betrug bereits 20 Monate. Vor der Behandlung war die Möglichkeit eines Phaeochromocytoms ausgeschlossen worden.

Hipertensión esencial en una niña de 12 años de edad tratada con compuestos de hexametonio.

Se describe el caso de una niña de 12 años de edad que sufría de una hipertensión maligna, grado IV, tratada con compuestos de hexametonio, con magníficos resultados. La presión arterial bajó a valores normales y desaparecieron todos los síntomas de la enfermedad, incluso las alteraciones de la retina. La niña llevaba ya 20 meses de tratamiento. Antes del tratamiento se excluyó la posibilidad de un feocromocitoma.

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Received 6.3. 1953.

Binnengasthuis
Amsterdam C.

Acta Pædiatrica **42**: 576—588. Nov. 1953

SUMMARY OF SUPPLEMENTS

Determination of Standard Energy Metabolism (Basal Metabolism) in Normal Infants

by PETTER KARLBERG

Acta Pædiat. 41, 1952, Suppl. 89

The methods for determining the energy metabolism under standard conditions has long been established in clinical work, as far as adults and older children are concerned. However, it has not proved applicable to infants.

A great many scientists have made a study of the energy metabolism in infants since the initiation of metabolic research, and this has been mainly by means of indirect calorimetry. A brief survey of the literature is submitted.

A careful examination of the methods applied has shown that none are immediately applicable to routine clinical practice.

A new method has been devised by the author. It is hoped that its simplicity should render it clinically useful. It is designed on the principle of the closed system. To the Krogh's spirometer, which is the apparatus used most commonly in Scandinavia for making determinations on adults and older children, is coupled a simple respiration chamber and a circulation pump. The carbon dioxide produced by a subject is reabsorbed by a soda lime filter built into the spirometer. Thus, only the oxygen consumption of a child will be determined. This is obtained from the gradual diminution of the volume of the system which is continuously registered on the kymograph of the spirometer.

The decrease in the volume in the system will equal the oxygen consumption of a subject only when gas equilibrium (temperature, humidity and carbon dioxide concentration) has been achieved. For this reason, a preliminary period of about half an hour is required. Because of the fact that an infant consumes considerably less oxygen per time unit than adults or older children, the actual observation period must be prolonged for about 30 minutes in order to secure sufficient accuracy. Accordingly, an investigation will take about an hour. It can be easily performed by a single person.

On account of the construction of the apparatus, no special contrivance for registering the movements of a subject is necessary. Such movements will be obtained from the kymographic curves.

A constant fall in the kymographic curve, while a subject is at rest, will

serve as a criterion of gas equilibrium in the system, and the decrease in volume will equal the oxygen consumption of a subject. This has been checked in 80 investigations, against the temperature in different parts of the system and the humidity in the respiration chamber.

The reliability of the apparatus has been checked by alcohol tests.

Suitable investigation conditions, including the physical condition of the subject, food and time of day have been discussed. It has been found advisable to make investigations on children in the morning or early forenoon, in a fasting condition, and in order to calm the subjects during the period of the observations a dose of barbituric acid preparation is administered as a sedative. The preparation, hexobarbital, has been used in doses that have not affected the energy metabolism. The author's investigations have shown that there is a 24-hour rhythm in the energy metabolism. Consequently, it is essential that the investigations are performed at a certain time in the day, in order to establish comparable investigation conditions. The morning or early forenoon have been chosen in the present work.

The conditions applied to investigations on infants are not altogether comparable to those affecting adults and older children, i.e. the so-called basal conditions. Nor can they, in fact, be regarded as true basal conditions. Therefore, the values obtained by the present method have been stated to refer to standard and not basal metabolism.

The random error of the method, reflecting errors in the oxygen consumption and minor dissimilarities in the investigation conditions, as well as individual variations from day to day, has been calculated from the differences between duplicate determinations. It has been found to remain at $\pm$ 0.073 lits. O_2/hr. At an oxygen consumption of 2 lits./hr., this will amount to $\pm$ 3.6 per cent and at 4 lits./hr. $\pm$ 1.8 per cent.

Investigations of the influence of food on the oxygen consumption of infants have shown that by the present method the so-called "specific dynamic effect" can be ascertained.

For an analysis of the energy metabolism from the oxygen consumption of the infants, a mean value of 15 per cent for protein metabolism has been applied, and a mean value of 0.86 for the respiratory quotient. The latter value has been obtained from a summation of values from investigations on infants available in the literature. The error introduced by this approximation yields a 95 per cent confidence interval to a maximal value of $\pm$ 2 per cent.

The range of applicability of the method is as follows: Determination of standard energy metabolism in infants aged from 1 week to 1 year, and if the child is small enough, up to 2 years. In order to secure satisfactory reliability in routine clinical work, children exceeding a body weight of 2.5—3.0 kg have been excluded. In addition, the respiratory quotient is taken to lie within normal variations.

By the present method, normal material consisting of 60 children aged from 8 days to 1 year has been investigated. Their physical development has been checked by means of a Swedish growth chart, worked out by the present author and co-workers. The material has disclosed no difference between boys and girls.

In order to correlate the energy metabolism with the body size, the latter must be represented by a suitable correlation factor. The correlation factors used in the literature have been examined.

The author has tested the correlation between the energy metabolism and the body weight in the general equation

$$C = W^b \cdot k$$

(C = Calories, W = weight, b and k = constants)

The exponent of the weight (b) has been found to be about 1 in the author's material, as well as in the available comparable materials in the literature. This explains why the simple rule of expressing energy metabolism per kg body weight has proved so useful in its application to infancy. In the older infants, the exponent b decreases and this change of the value of b becomes more obvious as the child approaches adolescence, to judge from Benedict-Talbot's big child material from birth to puberty. The exponent approaches more and more the $^3/_4$ found by Kleiber. This value applies to different-sized adult homeotherms, i.e. from mice to cattle. The higher exponent noted during infancy must be due partly to the influence of growth on the energy metabolism. This gradual change in the exponent b is observable already in infancy, and it invalidates to some extent the use of the body weight as a single correlation factor.

Nor is weight, as a single variable, suitable as a correlation factor, seeing that all individuals are assumed to possess a mean physical constitution. This will involve an approximation.

Since the relationship between weight and height gives an estimation of the physical constitution of an individual, it follows that when these two body measurements are combined they may constitute a better correlation factor with regard to the energy metabolism.

The relationship between the energy metabolism, on the one hand, and the weight and height, on the other, has been described by an equation of the form

$$C = W^b \cdot H^a \cdot k$$

(C = Calories, W = weight, H = height, b, a and k = constants)

By attributing different values to the exponent b and a, a variety of dif-

ferent formulae has been obtained. This procedure has been tried in the present material, as well as in the only comprehensive material traceable in the literature, that of Benedict-Talbot and Levine et al.

A multiple regression analysis has shown that this method is significantly better than using the weight or the height separately. The residual standard deviation has decreased to 5.1 per cent from 6.6 per cent, and from 9.5 per cent, when weight alone and height alone are applied as variables, respectively. For the American material this is less pronounced, since the residual standard deviation round the regression plane, expressed in the equation, is as big as 11.2 per cent.

This regression, in fact, does not even appear to be quite rectilinear, as judged from a constructed 3-dimensional model with logarithmic axes for each material. For the older infants, the regression plane betrays a certain curvilinear tendency towards the weight-height plane. The regression equation obtained by the above-mentioned procedure must therefore be handled with the same care in the case of the older infants.

An attempt has been made to extend the applicability of one single regression equation to the whole infant period.

In order to escape this approximation for the correlation factor, a new one has been tried, viz., the electrical capacitance of the body surface. With a view to practical use, a nomogram has been devised according to which the "capacitance surface" is obtained from weight and height. As far as the author's material is concerned, the relationship between the energy metabolism and the above-mentioned "capacitance surface" is found to be rectilinear. The residual standard deviation is about the same size, as in the multiple regression analysis.

Both these procedures have been employed in the compilation of values from the author's normal material.

Among normal values for infants recorded in the literature, under conditions approximately similar to those in the author's material, Kestner-Knipping's normal tables stand alone and are based on an age factor and a weight factor, together with Levine-Marples' analysis of Benedict-Talbot's material from 1921.

In a comparison with the above-mentioned materials, the author's material reveals a fair conformance to the American material, as far as small infants are concerned, while in the case of the older infants the author's material gives about 12 per cent lower values. When all the infant period is taken together, the difference between the two materials is significant. Compared with the values recorded by Kestner-Knipping, the values for the youngest children in the author's material are higher and for the older infants they are approximately similar.

The difference from the American material could be explained easily by the

dissimilarities in the investigation procedures. The present author investigated the children in a fasting state in the morning or early forenoon, while the Americans have given the children a small meal before the investigations, and they performed their observations during the middle of the day or somewhat later. Both of the latter conditions will increase the energy metabolism. Benedict-Talbot's child material from birth to puberty, emphasizes in its entirety the significance of this difference in the investigation conditions. At a body weight of about 16 kg, the investigation conditions are more similar to those used for infants by the author. At this point, their values fall.

The difference between the younger infants and Kestner-Knipping's standard values is more difficult to judge, since no original values for the energy metabolism have been given and there are no data regarding their investigation conditions.

The values obtained from the author's normal material have been used to form two nomograms for predicting the standard energy metabolism for infants from 1 week old to 1 year old. One was based on the multiple regression equation, the other on the "capacitance surface". In both instances, the body size of a child is represented by its weight and height.

As an application of the method, infants with untreated and treated hypothyroidism were examined.

It is not quite suitable to use the above-mentioned method employing the closed system to determine the energy metabolism of newborns. Since the respiratory quotient varies during the first week of life, both the oxygen consumption and the carbon dioxide should be determined. The energy metabolism of these infants is low and the reliability of this method decreases the smaller the child is. Besides this the variations in the respiratory exchange occur so rapidly that the observation period has to be as short as possible. To overcome the above-mentioned difficulties the author has devised an open circuit method, in which a small respiration hood covers the child's head alone. The gas analysis is recorded continuously by a "Gaswechselschreiber" according to Rein. Alcohol tests have confirmed the reliability of this method. Determinations made on children more than one week old have shown uniform results, when either the open or closed systems are employed.

Determinations made on newborns have shown that the method is suitable for studying the energy metabolism in newborns. Some examples are given.

Cystine Storage Disease with Aminoaciduria and Dwarfism (Lignac-Fanconi Disease)

by H. BICKEL et al.

Acta Pædiat. 42, 1953, Suppl. 90

Fourteen children suffering from cystine storage disease with aminoaciduria (Lignac-Fanconi disease) have been studied in the last 3 years, and the results are described in a series of eight papers of which the first paper contains a short review of the literature, some general remarks on aminoaciduria, cystinuria and cystine storage, and a brief statement on some of the results obtained and conclusions reached.

Publications by Lignac, Fanconi, Beumer and Wepler, and others, as well as our own observations, lead us to the conclusion that Lignac's disease (cystine storage disease) and Fanconi's syndrome of childhood (nephrotic glycosuric dwarfism) are one and the same disease. At the present time this disease cannot be identified with similar syndromes in which cystine storage has been excluded.

The variability of nearly every symptom in Lignac-Fanconi disease is stressed. The most reliable diagnostic features besides dwarfing are cystine storage and aminoaciduria of a characteristic pattern. Cystine storage can be demonstrated in vivo by slit-lamp investigation in cornea and conjunctiva, as well as in bone marrow and lymph glands, and the cystine can be identified in biopsy material by microscopy, X-ray crystallography and chromatography.

The aminoaciduria is accompanied by aminoacidaemia, and the characteristic pattern in urine is best shown by paper chromatography. The differentiation from other forms of aminoaciduria, such as that of newborn infants and classical cystinuria, is discussed.

Reasons are given why cystine storage and aminoaciduria are regarded as the result not of kidney dysfunction but of a prerenal disturbance of the whole aminoacid metabolism, probably situated within the reticulo-endothelial system.

Lignac-Fanconi disease has often been described in siblings but never in different generations. Our findings in the families of eight patients, including chromatographic studies of 138 urine specimens, confirm these observations. Of a total of 19 siblings four were probably and one certainly affected. No other relatives suffered from the disease. Consanguinity was found in one family; its incidence also seems to be raised in the literature. The data suggest that Lignac-Fanconi disease is genetically determined and of simple Mendelian recessive character, but that it is not genetically related to classical cystinuria or to the so-called Fanconi syndrome in adults. The frequency of Lignac-

Fanconi disease in the general population is estimated to be roughly 1 in 40,000 with a gene frequency of 1 in 200. The genetical prognosis is believed to be 1 in 4 for any subsequent child of parents who already have one sick child. Corresponding figures are given for cousins of the patient and for children of the patient's sibs.

Clinical manifestations of Lignac-Fanconi disease are dwarfing and wasting, rickets and osteoporosis, pyrexia, eye changes, sometimes with photophobia, vomiting, polydipsia and polyuria, dehydration, acidosis, sometimes tetany, states of profound collapse and even sudden death. Acute and chronic forms of the disorder are described.

Laboratory investigations reveal aminoaciduria, glycosuria, and sometimes albuminuria and ketonuria. In the plasma there is aminoacidaemia, evidence of acidosis, hypopotassaemia, mineral changes as seen in rickets, and perhaps hypocalcaemia and uraemia, which may be renal or extrarenal.

In a short factual analysis the phosphorus-calcium, protein, electrolyte and sugar metabolism as well as liver and kidney functions are discussed. A special section deals with E.C.G. changes, and electrophoretic investigations are described in an addendum.

The diagnosis "Lignac-Fanconi disease" should be suspected in all stunted children whose dwarfing is not obviously the result of other causes. Rickets, sometimes with severe deformity, evidence of kidney dysfunction and glycosuria are further clinical features, while the discovery of cystine storage and the demonstration of aminoaciduria with a characteristic aminoacid pattern provide final proof of Lignac-Fanconi disease. Differential diagnosis from renal rickets, resistant rickets, coeliac disease, renal acidosis, galactosaemia and glycogen storage disease may sometimes be difficult.

Treatment of the rickets with massive vitamin D doses, of the acidosis with Albright's solution and of the hypopotassaemia with potassium salts has proved encouraging; acidotic and hypopotassaemic crises have ceased, the children gain weight and grow slowly, their rickets is cured and they are livelier. Perhaps the most striking effect of prolonged alkalinisation is the gradual disappearance of aminoaciduria.

The case records are given in an addendum.

The radiological findings in seven children with Lignac-Fanconi disease are described and compared with those in the literature.

Bone changes may be absent. When present, they are those of simple rickets or, in the more chronic cases, of long-standing late rickets. The appearances are non-specific and not distinguishable from those of avitaminosis-D or from "resistant" rickets.

These observations agree with theoretical conceptions because the bone

changes, contrary to previous belief, probably originate in a failure of intestinal absorption of phosphorus and calcium.

The ophthalmological appearances in five cases of Lignac-Fanconi disease have been studied. In every case crystalline deposits were seen in cornea and conjunctiva, in two cases in the iris, but never in the lens, vitreous or other media of the eye. Massive deposition was easily recognisable by loupe and may even be suspected by naked eye examination. In less developed cases the crystalline deposits were visible only by use of a slit-lamp; the application of this technique in uncooperative children is described.

Microscopy of a conjunctiva biopsy specimen revealed that the crystals were partly hexagonal, their localisation being intra- and extra-cellular. The ninhydrin test gave a diffusely positive reaction. X-ray diffraction photography of the biopsy specimen showed the pattern to be entirely characteristic of pure crystalline cystine.

In two patients with severe photophobia epithelial lesions of the cornea were shown by staining with fluorescin. This change was absent in the patients without photophobia and is in our opinion the immediate cause of the photophobia.

The eye appearances in Lignac-Fanconi disease are sufficiently characteristic to eliminate any serious diagnostic difficulty.

The case records of two brothers suffering from Lignac-Fanconi disease are given in detail. Two further siblings probably suffered from the disease. The results of certain special investigations are discussed. In a mineral balance we have not been able to prove that the hypophosphataemia in one of the cases was due to an excessive excretion of phosphorus.

In both brothers the glutamic acid level in the serum was found to be raised. This supports the view that a disorder of aminoacid metabolism is the underlying cause of the disease. It is suggested that the large quantity of aminoacids passed by the kidneys has a nephrotoxic action. The pathogenesis of other features of the disease can be explained by dysfunction of tubular reabsorption caused by this action, and the ultimate onset of renal failure can be explained by the same action involving the glomeruli.

With alkali therapy the general condition of both boys has improved, although a normal plasma CO_2 combining power could not be reached in either case. High vitamin D dosage has produced some healing of the skeletal changes, but attention is drawn to the possibly dangerous effects of this treatment. One case died from heart failure secondary to renal failure after three months treatment.

The genetics of the disease are discussed. The evidence presented from our cases seems to confirm the theory of a recessive inheritance.

Phosphorus and calcium balances in three patients of this series are analysed

and compared with eight balances in the literature. Four of the eleven balances were carried out under vitamin D influence and were positive. Of the remaining seven, five phosphorus and two calcium balances were negative. This was due to phosphorus and calcium loss in the faeces; neither hyperphosphaturia nor hypercalciuria was detected. The balances in Lignac-Fanconi disease were identical with a balance performed in a case of resistant rickets. Compared with renal rickets the hypocalcaemic, hyper- or normo-phosphataemic form of Lignac-Fanconi disease shows certain differences. Though the excretion of phosphorus and calcium in the urine was decreased in both conditions, the hypocalcaemia in Lignac-Fanconi disease was more marked and the hyperphosphataemia mild or absent. It is suggested that the mechanism of these biochemical changes is different from that in renal rickets.

Chromatographic studies of urine and plasma in patients with Lignac-Fanconi disease showed a moderate to strong increase of 10-20 aminoacids in the urine, while in the plasma the aminoacid pattern was normal though the concentration of the aminoacids seemed to be above the normal range. Microbiological assay of twelve aminoacids by Dr. Schreier showed up to a twentyfold increase of various aminoacids in the urine and up to 100 per cent increase in the plasma. Estimations of glutamine and glutamic acid by Professor Krebs showed similar results. These findings do not indicate primarily a renal mechanism of the aminoaciduria, but suggest a prerenal disturbance of the aminoacid metabolism.

Electrolyte studies in two patients under normal conditions and after acid feeding point to a complex disturbance of the acid-base metabolism. Several factors seem to be involved, namely, increase of organic acids in urine and probably in blood, insufficient ammonia production by the kidney, loss of the fixed bases sodium and potassium, and faulty reabsorption of bicarbonate. The relative importance of these factors is discussed.

No satisfactory explanation of the "glucose shock" in Lignac-Fanconi disease has so far been offered. During three glucose tolerance tests we followed the potassium level in the plasma of our patient and of a healthy control. Glucose ingestion resulted in pronounced and prolonged hypopotassaemia in our patient, which was not due to potassium loss in the urine. In the control the response was similar but milder and briefer. We suggest that the "glucose shock" in Lignac-Fanconi disease is a "hypopotassaemic shock".

Detailed gross anatomical and histopathological findings in six cases of Lignac-Fanconi disease are described and discussed. An attempt is made to present the natural history of individual organ changes, particularly those of the kidney. It is interesting to note that the disease in its early stages can occur without kidney changes. The bone changes are essentially rachitic; there is no feature of the histopathology of the bones which is not met with

in rickets, particularly in "rachitis tarda". Bone changes of hyperparathyroidism are not conspicuous in this disease. The parathyroids were markedly hypertrophic in two of our cases; hypertrophy in other cases cannot be excluded.

The phosphatase reaction was negative in all kidneys examined, reduced in liver, spleen and bone-marrow but normal in the small intestine. Negative phosphatase reaction in the kidney has also been found in chronic inflammatory kidney disease and is not specific for Lignac-Fanconi disease.

Methods for demonstration and identification of cystine crystals in tissue sections, bone-marrow films and lymph node imprints are described, together with experiments which account for the difference between the crystallographic appearance of cystine in tissues and cystine crystallized from aqueous solutions. In our opinion a lymph node biopsy is the most reliable procedure for a definite diagnosis of Lignac-Fanconi disease *in vivo*, though bone-marrow sections and/or films are usually sufficient for the purpose.

The intracellular localization of cystine crystals is stressed, and histopathological and experimental evidence is given for the assumption that cystine storage is not due to phagocytosis, but that cystine crystallizes at the site of its formation, namely in a certain part of the reticuloendothelial system.

A critical review is given of various hypotheses concerning the pathogenesis of Lignac-Fanconi disease. The hypothesis is put forward that Lignac-Fanconi disease is a disorder of protein metabolism, probably of its anabolic phase. As a disorder of intracellular metabolism, the disease is likened to true lipidoses.

Electrocardiographic Studies in Scarlet Fever. An investigation with special reference to the effect of penicillin treatment

by MAJ LEVANDER-LINDGREN

Acta Pædiat. 42, 1953, Suppl. 91

The *purpose* of this work has been to study the effect of penicillin on myocarditis associated with scarlet fever. This has been done by means of electrocardiographic examinations on concurrent groups of patients with scarlet fever treated both with and without penicillin. To accomplish this it has been necessary to make a thorough study of the electrocardiograms in order to differentiate between alterations resulting from acute myocarditis and others caused by physiologically normal variations, constitutional anomalies, or old lesions.

The *material* consists of 450 cases of scarlatina treated with penicillin, 440 controls who received no penicillin, and a concurrent group of 211 in whom the initiation of penicillin was delayed until the fifth hospital day. In addition there are two later treatment groups consisting of 707 patients altogether with an incomplete control group of 99. These cases, as well as a number in the desquamating stage and others with scarlatina from the same period, have also been included since they are of interest with regard to the electrocardiographic studies. Altogether the material includes 2,831 patients of whom 279 were adults.

Electrocardiograms were recorded serially and each series evaluated individually.

Even in patients whose hearts are not affected the electrocardiogram can be expected to vary more than ordinarily during an infectious illness with its different phases of sympathetic and vagus influence.

The normal electrocardiogram of the individual can be established after recovery (as a rule the myocarditis of scarlet fever is reversible). Stimulation of the sympathetic and vagus factors, "work"-electrocardiograms, and recordings of the electrocardiogram in various body positions have been employed in this connection to study the normal variability in different subjects.

A pathological alteration in the electrocardiogram can be considered to justify a diagnosis of myocarditis only if an association with the scarlatina can be demonstrated. On the other hand, a variation within the accepted normal limits may be an indication of myocarditis if it lies beyond the normal limits of variability for the subject in question.

Alterations apparently within physiological limits may also be due to a myocarditis. If, in addition, subjective cardiac complaints were reported the patient was included in a special group designated by "probable myocarditis with equivocal electrocardiographic changes and heart symptoms".

Alterations of the P wave have been analyzed. The majority of these were apparently due to minor changes in the position of the pacemaker (called "perisinus rhythms" by the author) and are physiologically normal in character. A definite intra-auricular conduction disturbance was present in only one case.

Coronary sinus rhythm or atrioventricular nodal rhythm have been observed in 43 cases. These have been analyzed with reference to whether they showed signs of being active or passive and whether they were associated with the scarlet fever. In these cases 8 were definitely active and have been interpreted as evidence of myocarditis, while 3 were of questionable nature. The others give impression of having been passive physiological wanderings of the

pacemaker associated with decreasing sinus frequency or increased vagus effect.

Premature systoles have been observed in 31 patients. Although 5 of these were pathological in character, only 1 of them displayed a definite association with a scarlatina myocarditis.

Parasystoles of the ventricular type have been diagnosed in 5 patients, and in one of them the cause seems to have been myocarditis.

Escaped beats of nodal origin have been observed in 9 patients. Ventricular escaped beats were seen in 2 cases both of whom have been considered to have myocarditis.

Auriculoventricular conduction disturbances have been regarded as resulting from myocarditis in 34 patients. Among these were 1 case of total block and 2 of grade II block. Four of the subjects with myocarditis had P-Q values within accepted normal limits, but the range of variation and the overall series of electrocardiograms in these cases indicated a temporary disturbance during the illness. Another 26 patients were found to have prolonged P-Q intervals; and 12, large variations in the P-Q time, although these remained unaltered over a period of one or several years. In 3 different families two or three siblings displayed prolonged P-Q times, and a constitutional anomaly is regarded as the probable explanation.

Changes in the T wave and the S-T segment. Changes in the T wave of various degrees which have been interpreted as evidence of a scarlatina myocarditis have been observed in 57 cases, and depressions of the S-T segment with the same significance have been found in 11 patients. In another large group of patients the alterations were found to have a possible connection with sympatheticotonic factors or changes in position.

Intraventricular conduction disturbances have been observed in 29 patients; but in only 2 cases, both of whom displayed an intermittent Wilson block, would a scarlatina myocarditis seem to have been the explanation. The remaining cases displayed no change during a long period of observation. Two pairs of siblings displayed similar alterations seeming to indicate the presence of a constitutional anomaly. Pre-excitation was found in 7 cases, although only 1 appeared to be related to the scarlet fever.

Certain cases of myocarditis with more marked changes in the electrocardiogram have been designated as "severe".

The effect of the frequency with which the electrocardiograms are recorded is demonstrated by the fact that the incidence of myocarditis diagnosed in a group of 208 patients rose from 3.9 per cent when the electrocardiogram was recorded once a week to 5.8 per cent when 3 recordings were made each week.

The *age factor* is illustrated by the significantly higher total incidence of myocarditis in adults than in children (11.5 per cent, as compared with 3.1

per cent) as well as the more "severe" electrocardiographic changes (5.0 per cent compared to 0.24 per cent).

Seasonal variations during a year show that the children have a probably higher incidence of myocarditis during the winter season compared with the summer. The same tendency was displayed by the adults.

A comparison between the cases receiving penicillin and the controls reveals that all groups of adults and all but one group of children receiving penicillin early in the illness, had a lower incidence of myocarditis than the control groups.

In the *adults* a statistical analysis of the individual groups revealed no significant difference. When 2 penicillin groups and their controls were combined the difference in the incidence of myocarditis between the penicillin cases and the controls rose to 11.8 ± 5.5 per cent. With regard to "severe" alterations the difference was probable -9.4 ± 3.8 per cent.

Patients who began to receive penicillin later in the illness reveal a higher incidence of myocarditis than those receiving early treatment but a lower one than the controls. The incidence of "severe" electrocardiographic changes in all of the adults receiving early penicillin treatment in the entire study is 0.84 per cent, while in all other adults—controls, desquamators, and those receiving late penicillin treatment—the incidence was 8.8 per cent. This difference is statistically significant.

In *children* the differences do not come up to a statistically definite value.

The *desquamating cases* display a lower observed incidence of myocarditis than the control cases. This is probably due to the limited period of observation for most of the desquamators. In a group of 107 patients in which the scarlet fever was complicated by the presence of *other infectious diseases* no definite difference as compared with the rest of the material could be established.

Summary: Penicillin is apparently able to reduce the incidence of "severe" electrocardiographic changes in scarlet fever, although it shows only a tendency to reduce the actual incidence of myocarditis in association with the disease.

Of course these observations and conclusions are valid only in milder epidemics of the sort seen in recent years. Should a more severe type appear, penicillin therapy would in all likelihood assume a greater importance with regard to myocarditis in both adults and children.

In view of the present findings regarding the incidence of myocarditis, early penicillin treatment should be instituted in *adults*. With regard to myocarditis in *children*, it would seem that with infections of the current mild type treatment may be omitted or delayed. This is of practical importance in regard to the tendency to development of recurrences following early treatment of scarlatina with penicillin.

The Iron-Binding Capacity of Serum in Infants and Children

by BENGT HAGBERG

Acta Pædiat. 42, 1953, Suppl. 93

Changes in the iron metabolism are reflected in the plasma and can be estimated from fluctuations in the iron-transporting plasma protein, transferrin, and its amount of attached iron, the serum iron.

This study refers to investigations on the serum iron and the total iron-binding capacity of the transferrin in about 300 infants and children. Special emphasis has been laid on the physiological changes occurring during infancy, when the amount of storage iron changes more than at any other time in later life. The iron stores, satisfactory at birth, increase during the first two months, but thereafter fall successively, remaining small during the next few years.

In estimating the total iron-binding capacity, the iron-saturated fraction (the serum iron) and the unsaturated fraction (the unsaturated iron-binding capacity) were determined independently and added together.

For the determination of the serum iron a modification of the method of VAHLQUIST (1941) was used and found sufficiently accurate. Only 0.3 ml of serum was needed. Instead of filtering, the sample was centrifuged after precipitation of the proteins.

The unsaturated iron-binding capacity was determined according to the method of RATH & FINCH (1949), which is based on the fact that the salmon-red iron-transferrin colour deepens on fractionated addition of iron until full saturation is attained. This method was found to have definite limitations. It was unreliable in lipaemic sera or sera with discoloration or severe disturbance of the plasma protein pattern. If the concentration of bilirubin exceeded 3—4 mg per cent the estimation could not be satisfactorily performed, whereas slight haemolysis did not interfere with the result. In spite of its disadvantages the method was, however, found to be accurate enough for the special purposes of this investigation, a fact proved by iron tolerance tests.

A simple 'one stage measurement' of the total increase in extinction after supersaturation with iron was found to give too unreliable values, probably owing to the presence of variable amounts of substances interfering with the development of the iron-transferrin colour. Possibly due to the same mechanism an average introductory iron enrichment of 15 gamma per 100 ml was found to be necessary to obtain any increase in extinction at all.

1. The average serum iron level in 54 healthy adults (26 men and 28 women) was 130 ± 5.2 gamma per cent, and the corresponding total iron-binding capacity 330 ± 4.9 gamma per cent. These figures served as basic values for judging the results obtained in infants and children.

2. The serum iron of the umbilical cord at parturition was as high as 173 ± 6.9 gamma per cent, whereas the total iron-binding capacity was 259 ± 10.5, *i.e.* significantly less than in healthy adults. The changes parallel a stage of active storage of iron, and are in striking contrast to the pattern in the serum of the mothers, in whom there is mobilization of iron from the depots.

3. Infants $^1/_2$—2 months of age are in a state of physiologically suppressed erythropoietic activity, which implies a diminished need and hence increased storage of iron. They showed a still lower total iron-binding capacity, 212 ± 6.6 gamma per cent, and an average serum iron of 142 ± 7.1 gamma per cent, *i.e.* significantly less than at birth but still high. It is notable that the relative saturation with iron was the same as in cord blood.

4. Infants aged 2—6 months, the period of return to full erythropoietic activity during which increasing amounts of iron are mobilized from the depots, had a falling serum iron (113 ± 5.6 gamma per cent at 2—4 months, and 78 ± 6.1 at 4—6 months) and a rising total iron-binding capacity (308 ± 11.3 gamma per cent at 2—4 months, and 360 ± 12.5 at 4—6 months).

5. The serum iron values in infants and children of $^1/_2$—3 years remained low, with an average of about 95 gamma per cent, and the total iron-binding capacity was markedly elevated, with an average of about 390 gamma per cent. It is at these ages that the iron stores are minimal, and the children are particularly vulnerable to even small additional strains on the iron balance. The values obtained put in relation to the haemoglobin level also suggested that some cases with slight iron deficiency anaemia were included in a 'normal' series in spite of haemoglobin values within accepted limits.

6. The values in older children successively approached adult levels, which were attained more rapidly by the serum iron than by the total iron-binding capacity.

7. A series of 16 children with iron deficiency anaemia had an average serum iron of 50 ± 6.5 gamma per cent, and a total iron-binding capacity of 496 ± 7.1 gamma per cent.

8. The general conclusion was that in infants and children the level of the total iron-binding capacity and its saturation with iron closely reflects the probable direction of the plasma iron transport, *i.e.* the storage and mobilization of iron, and thus usually also the size of the iron depots. The findings clearly support LAURELL's hypothesis concerning the regulation of the plasma transport of iron.

9. The metabolism of iron is disturbed during infection. The disturbance

is revealed by a simultaneous fall in the serum iron and total iron-binding capacity. This pattern of change deviates from the physiological outlined above.

From studies in 82 children suffering from various acute infections it was found that the extent and rate of the fall in total iron-binding capacity was mainly related to the severity of the infection. It developed successively during the first week, and reached a level of equilibrium which remained constant in infections with a protracted course. The return to normal seemed to occur gradually within the week following recovery.

It was also found that the changes in serum iron generally occurred more rapidly than those in the total iron-binding capacity. This confirmed earlier assumptions that the lowering of the total iron-binding capacity does not cause the hypoferraemia of infection.

The Long-Term Prognosis for Prematurely Born Children

by INGVAR ALM

Acta Pædiat. 42, 1953, Suppl. 94

It is evident from the review of the literature that opinions regarding the mental and physical prognosis for prematurely born children are at variance, as are the figures obtained in the different investigations. This is presumably due mainly to the differences in the respective series with regard to such factors as the social status and post-natal care and to the fact that the series were often small and comparisons were seldom made with comparable control series.

The present series of prematures consists of 999 boys with a birth weight of 2500 grams or less, born at the three largest maternity hospitals in Stockholm between 1902 and 1921. They were all born in wedlock and were discharged alive from hospital. The control series consists of 1002 so-called social twins with a birth weight between 2760 and 3750 grams.

Comparisons are, as a rule, made between the following three series: 1. 759 premature single-born children; 2. 240 premature plural-born children; 3. 981 single-born controls.

An account of the obstetric, paediatric and social conditions is given. On the whole it confirms already established facts, but also serves as a basis for the subsequent steps in the investigation. A summary of these conditions is recorded. The mortality among those children discharged alive from the maternity hospitals is reported as follows:

A. As could be expected, the mortality rate is higher for the prematurely born children than for the controls, even though all the children were discharged alive from hospital. The difference in the mortality is greatest during the first months of life and does not become evened out until 2—3 years of age. The difference is caused mainly by a considerable excess mortality from infectious diseases among the prematurely born children. The mortality is highest among those in the lowest birth weight group, those in the lowest social group, those whose mothers were ill during pregnancy and those with several older siblings.

B. A comparison between the single-born and the plural-born prematures discloses the surprising fact that the mortality is consistently higher for the plural-born children. This difference between the two series of prematurely born children is statistically probable, both for the total mortality and for the mortality from infectious diseases. In social group III, the difference is statistically significant. The higher mortality rate for the plural-born premature children as compared to the single-born prematures applies when the birth weight is the same in both categories when the condition of the mother during pregnancy is the same and with the same birth order number.

An account is given of certain physical and mental deviations from the norm, *i. e.*, mental developmental disturbances, diseases resulting in mental or physical disablement and tuberculosis. Only the percentage figures are given here, as well as the differences between the single-born prematures (1) and the single-born controls (3).

A. *Mental develpomental disturbances*

	1	2	3
		Per cent	
a. Pupils in Special Classes	3.3	5.8	1.7
Difference 1–3: not significant.			
b. Institutional care	4.8	2.1	1.2
Difference 1–3: statistically significant.			
c. Pensions: spastic paralysis, epilepsy, educable and ineducable mental deficiency	3.5	2.8	0.7
Difference 1–3: statistically significant.			
n. b. the same individual is frequently recorded under a, b, and c.			

B. *Disabling physical diseases*

	1	2	3
		Per cent	
Other illnesses than those under A entitling to a pension	3.1	0	3.0
Difference 1–3: not significant.			

C. *Tuberculosis*

	1	2	3
		Per cent	
a. Morbidity	11.0	14.6	13.0
Difference 1–3: not significant.			
b. Mortality after 1 year of age	3.6	2.8	3.8
Difference 1–3: not significant.			

The physical development at adult age and the fitness for military service are evaluated on the basis of the notations in the military registers.

	1	2	3
		Per cent	
a. Fully fit for active service	56.2	62.6	63.8
Difference 1–3: not significant.			
b. Unfit for active service	17.1	15.3	12.5
Difference 1–3: not significant.			
c. Military promotion of those fully fit	15.0	4.9	12.3
Difference 1–3: not significant.			
d. Mean height at 20 years of age	172.8 cm.	172.9 cm.	175.6 cm.
Difference 1–3: statistically significant.			
e. Mean body weight at 20 years of age	64.0 kg.	65.0 kg.	67.0 kg.
Difference 1–3: statistically significant.			

The social and economic prognosis is assessed from several aspects. In the following table, the majority of the data are given as the percentages.

	1	2	3
		Per cent	
a. The social group of the subject:			
Social group I	10.1	10.8	12.4
Social group III	45.6	50.0	43.6
b. Various forms of public relief:			
Unemployment relief	16.9	21.3	14.6
Poor relief	20.4	22.3	21.8
Sickness relief	10.2	10.7	12.1
Other relief	17.1	23.3	18.1

Here as well, it must be recalled that the same individual may have received more than one form of relief.

	1	2	3
c. Median for net income in Swedish crowns	6080	5900	6270
d. Convictions for crime per cent	5.8	3.5	8.5
Convictions for drunkenness per cent	11.0	15.3	10.9

There are no statistically significant differences between 1 (premature single-born children) and 3 (single-born controls) with regard to any of the social and economic conditions listed in the aforegoing.

Thus, a comparison is made between a relatively uniform series of prematurely born children, whose initial social status was not markedly poor, and a control series of children for whom the conditions were similar to that of the prematures in most respects, but whose birth weight was normal. Such a comparison permits the following conclusions to be drawn, at any rate with regard to the present series:

1. The mortality rate is considerably higher among the prematurely born children during the first two years of life, particularly among the plural-born prematures.

2. Among those prematurely born children who survive the first two to three years of life, there is a moderately higher incidence of such disorders that are usually considered to be associated with birth injuries than among the controls. The difference is statistically significant. In other respects, and with regard to other disabling diseases and tuberculosis, there is no difference between the prematurely born children and the controls.

3. There is a statistically significant difference between the height and body weight at 20 years of age in the two categories, the figures being lower for those prematurely born than for the controls. The incidence of those able to do their military service is practically the same in both categories and those prematurely born performed their military duties, on the whole, as well as did the controls.

4. As regards social adaptation, there are no statistically significant or probable differences between the prematurely born children and the controls. The general impression is that under no conditions were they more of a burden on the community than were the controls and that, in the majority of respects, they did as well as the controls.

Acta Pædiatrica **42**: 595—598. Nov. 1953

Proceedings of the Section for Pediatrics and School Hygiene of the Swedish Medical Society

Meeting, May 15, 1953.

A. Dahlström and H. Gladnikoff: **Case with leucemic blood picture.**

L. Ström: **Trauma and tuberculosis—experimental studies.**

H. O. Mossberg: **Acute cerebellar ataxy in children.**

Reference was made to the literature concerning acute cerebellar ataxy among children. Two cases were described. The first was a girl aged three years and nine months where the cerebellar ataxy came on suddenly and was the sole introductory symptom of the illness and where the patient had recovered completely in a month. The second was a boy of one year and nine months who during the course of a few days developed cerebellar atactic symptoms but in addition had unusually severe tremors of the whole body which could be taken as indicating an extra-pyramidal tract lesion. Recovery occurred very slowly in this case and even five months after the onset of the illness he showed some evidence of disturbance in gait, while the tremors had disappeared completely. Etiologically influenza could not be excluded since at the time of the onset of the patients' illnesses this infection was present among the population and both patients exhibited complement fixation reactions, indicating that they had suffered influenzal infection.

M. d'Avignon, J. Husby and L. Widén: **Acute progressive encephalitis.**

(To be published in Acta pædiat.)

R. Lundström: **Prophylactic use of gamma globulin in infections.**

A short survey is given on the current position with regard to the use of gamma globulin. Experience in other countries has shown that, subject to certain conditions, the preparation is an effective prophylactic in measles, infectious hepatitis, and poliomyelitis. There are also indications that convalescent serum is the most suitable basic material for the production of gamma globulin intended for prophylaxis against mumps and German measles. In prophylaxis against whooping cough, the basic material should consist of serum from persons hyperimmunized against the disease. Gamma globulin has been tested therapeutically in a number of other diseases, but its effect hitherto has not been proved. Some experience with convalescent serum in the treatment of infectious mononucleosis indicates the possibility of obtaining some effect with gamma globulin produced from such serum.

Meeting at Uppsala, June 6, 1953

Å. Gyllenswärd: **A case of congenital heart block.**

A brief account was given of a case with a heart rate at birth of 38. The intrauterine rate was about 30. Electrocardiography verified the diagnosis of a total block. At an age of 2 months, the child is still in an excellent condition, satisfactorily increasing in weight. The heart rate was unchanged at about 40.

Martin H:son Holmdahl: **Malignant tumours in all four children of the same parents.**

A predominantly hereditary etiology is supposed to occur only in certain comparatively rare forms of tumours, such as retinoblastomas, malignant degeneration in xeroderma pigmentosum, neurofibromatosis and polyposis intestinalis. Other cases of a familial occurrence of malignant tumours can often be explained from the presence of a common exogenic etiologic factor. The tumours are then, as a rule, of the same nature and localized to the same organ. In the case of the present brothers and sisters, with their malignant tumours differing in all four, a genetic factor seems to be indispensable for an etiologic interpretation. No accumulation of tumours has been noted in the immediately preceding generations; nor does any excess mortality in the family occur. The disease histories of the children run briefly as follows:

1. A boy. Born in 1943. Fell ill at an age of 8 months with symptoms of increasing intracranial pressure. Increasing hydrocephalus. Died 10 months old. Patho-anatomic diagnosis: *Glioma permagna hemisphaer. sin.* (*Medulloblastoma*).

2. A girl. Born 1944. Healthy up to the age of 7 years. Aching and swelling below left knee. Roentgenography disclosed *osteosarcoma* in the fibula. No metastases observed in the lungs. Amputation at the middle of the femur. Without troubles for 10 months. Then successively increasing respiratory and neurologic symptoms. Died a year after the onset. Postmortem showed osteosarcomatous metastases in the lungs and at the base of the skull. It further revealed a quite new histologically malignant tumour, viz., an *ependymoblastoma* in the left ventricle of the brain.

3. A boy. Born in 1945. At the age of 3 years had vomiting fits and convulsions. An investigation disclosed a right-sided expansive intracranial process. At operation a glioma in the parieto-occipital region was evacuated. Patho-anatomic diagnosis: *Spongioblastoma multiforme.* Died six months later. Postmortem showed a local recidivation and tumour metastasis to the subarachnoidal space.

4. A girl. Born in 1950. At birth, a knot, big as a pea, in the lower lip. Under examination, when the second child beecame ill. The tumour was then the size of a hazel-nut, hard and adherent to the skin. It was extirpated. Patho-anatomic diagnosis: Malignant tumour probably a *rhabdomyosarcoma.* The girl is now, $1^1/_2$ year after the determination of the diagnosis, healthy, without a sign of any local recidivation or metastases. In none of the four children have any malformations or other abnormalities been observable during the clinical examination or the autopsies.

Å. Gyllenswärd: **Ulcerative colitis and hepatic injury.**

T. Skoog: **Early radical operation of congenital torticollis.**

(To be published elsewhere.)

The method, according to BROWN, for excision of the sternocleidomastoid muscle was described. Emphasis was laid on the vicinity of the cicatricial formations to the accessory nerve and the big cervical vessels. Free-laying of the muscle from two transverse skin incisions was recommended. When the operation is performed early, a secondary deformity is prevented and such scoliosis and asymetry as are to be found can be corrected during the period of growth without any after-treatment with plaster or other bandages. On account of the tendency to spontaneous healing in the case of some of these injuries at the time of birth, it is not advisable to operate until after the first year of life. Accounts were given of seven cases. Six were operated upon at an age of 2—6 years. The period of observation covered, on an average, $1^1/_2$ years. In three cases, the but inconsiderably changed sterno-mastoid muscle body was left untouched. In two of these cases, total myectomy was performed after a year, on account of remaining reduction of movability. In all these cases, a normal position of the head and free movements were achieved. No disturbing defect in the neck contour was to be found. Breech presentation was recorded in 4 cases. In 1 case forceps was resorted to. In another case the delivery was normal. In one instance, no data regarding delivery were obtainable.

B. Hagberg: **Hodgkin's disease in infancy and childhood.**

Hodgkin's disease may occur at all ages, though children below 10 years of age are affected at a rate of only 5—10 per cent. During the first years of life, the disease is probably very uncommon. There are, however, descriptions available of cases in newborns. A characteristic feature is a much more marked preponderance for the male sex before than after puberty. Thus, among children no less than about 85 per cent are boys. The clinical picture does not differ in any essential respect from that in adults. Nor is any definite difference to be noted with regard to the average duration of the disease before death. Still, such forms of the disease as show a very malignant course would seem to be comparatively more frequent among children. Six cases are described, all boys, of an age of from 5 to 12 years. Two of the boys died within three months of the onset, two after 1—$1^1/_2$ years, one after 6 years. One boy is still living. An atypical clinical course was noted in a boy of 9 years. He fell ill with an encephalitic syndrome with convulsions, neurologic findings and pyrexia, but without any enlarged superficial lymph nodes or any splenic enlargement. Strangely enough, at the post-mortem three months later, no sign of any lymphogranulamatous changes was detected in the central nervous system. Another case revealed an ulcus ventriculi. In a third case, the clinical picture was at times dominated by a considerable exudative pleurisy.

(To be published more fully in Nordisk Medicin.)

R. Berfenstam: **Prevention of accidents to children. Studies in England and the Netherlands.**

While the death-rate in practically all diseases of childhood has fallen considerably during the past few decades, no similar tendency has been traceable in the group of "violent deaths". 400—450 children die every year in Sweden owing to accidents. A fourth are traffic accidents, a third are drownings: the so-called home accidents being responsible for the remaining deaths. Throughout, the high risk of death in infancy is striking. In the first 5 year age group, the number of deaths equals that of

the two following 5 year groups taken together. It is also worth noting that boys are more often victims of accidents than girls. It is difficult to estimate the total number of accidents among children in Sweden. A probable estimate is about 100000 per annum of such a degree of severity as to call for medical assistance. There are organizations in Sweden for the promotion of safety in traffic. Now and then, campaigns are started with a view to reducing the number of home accidents. Still, this preventive work must be intensified. From a study of the frequency of fatal accidents in other countries and their preventive efforts, important conclusions can be drawn. The Netherlands report a somewhat higher figure of accidental deaths than does our country. Preventive measures are being tried. As yet, however, they have perhaps not been sufficiently brought home and impressed on the public mind. In England, on the other hand, this problem has attracted a general attention. It forms part of the medical study and is the subject of continual research. We ought to cope with this task in a similar way, trying, among other things, to form an organization which, after the pattern of the English, by means of useful propaganda and with the assistance of doctors, nurses and other interested professional groups, would be able to prevent accidents both at home and in the streets.

Acta Pædiatrica **42**: 599—601. Nov. 1953

BOOK REVIEWS

Ronald S. Illingworth: **The Normal Child. Some Problems of the First Three Years and Their Treatment.**

J. & A. Churchill Ltd., London, 1953. 342 pp. Price 30 s.

The author, who is professor of child health at the University of Sheffield, presents an outline of normal mental and physical development of children in the first 3 years of life placing emphasis on its physiological variability. He discusses problems, often of minor importance medically but of serious import to mothers, such as behaviour problems or feeding disorders. These are either not mentioned at all or treated very superficially in the ordinary textbooks of pediatrics. He stresses the influence of emotional factors in normal development and discusses the many sources of worry for a mother, who has recently given birth to a child. An excellent description is given of "3-months colic". His conclusions that rumination is a serious problem with a not inconsiderable mortality does not exactly correspond to the opinions held by Scandinavian pediatricians. What he writes about the evaluation of the body weight will certainly be accepted by everyone: "When a doctor is faced with an otherwise well child, who on account of constitutional reasons is smaller than the average, he should limit his efforts not at trying to alter the physique but at trying to persuade the parents and others to accept him as a normal child." Using good judgement he stresses that the diagnosis of mental deficiency should not be made or suspected on account of retardation in a single area of development. His description of the need for love and security and their importance in the prevention of behaviour problems is written concisely and well and should be read by all parents and physicians. This book can be recommended without any reservation.

Georg Henneberg: **Weg, Ziel und Grenzen der Streptomycintherapie.**

Walter de Gruyter & Co., Berlin, 1953. 287 pp. Price DM 26.

This volume which is No. 3 of "Aktuelle Fragen der Inneren Medizin", contains a summary of the experiences of the streptomycin-treatment of tuberculosis and other diseases at the clinics in Berlin. It is to be regarded as the report of the Berliner streptomycin committee (Henneberg, Jauerneck, Joppich, Mader, Marcuse, Misgeld, Nohlen and Oettel). Although there have been very many books written on streptomycin therapy, this volume is of interest because it gives an account of the opinions and experiences of the German clinicians. Of special pediatric interest are the chapters on tbc meningitis in childhood and streptomycin therapy in non-tuberculous diseases of children. Treatment of tbc meningitis conisted of the following: a) intrathecal streptomycin therapy administered once a day for the first 3 months, and then twice weekly (30 mg), b) intramuscular streptomycin injections given twice daily (20—30 mg/kilo). Both treatments were carried out simultaneously over the entire course of the disease. Immediate prognosis showed a mortality rate of 57.7 %. Combined treatment with PAS or other compounds was not used.

Centre International de l'Enfance: Réunions et conférences: III. Les antibiotiques et les maladies de l'enfance.

Librairie Le François, Paris, 1952.

This volume presents papers and discussions from an international conference held in Paris in 1952. Among the 90 participants representing 16 different countries there were many well-known clinicians and bacteriologists such as Hatty Alexander, C. Cocchi, Robert Debré, G. Fanconi, Alexander Fleming and L. P. Garrod.

The first part of the book deals with antibiotic treatment of various infectious diseases. It is maintained that all treated cases of purulent meningitis can be saved if the diagnosis is made in time. The importance of wider indications for spinal tap is stressed, especially with infected infants. The staphylococcic infections in hospitals are nowadays to a great extent penicillin-resistant but are often sensitive to chloromycetin. All types of hemolytic streptococci are still penicillin-sensitive. Combined antibiotic treatment is generally inconvenient and in most cases debatable. As a rule, however, it is recommended in tuberculosis, where complications of this disease may be treated with streptomycin together with PAS and/or INH.

The second part of the book discusses the function of the laboratory in antibiotic treatment. The importance of a correct etiological diagnosis and the determinations of the degree of bacterial resistance is stressed. It also discusses the value of collaboration between the laboratory and the clinician in order to transfer the results of the laboratory examinations to the benefit of the patient. The doses of the newer antibiotics, their method of administration, blood- and urine concentrations and their side-effects are dealt with in some articles. The conference expressed the opinion that the reports of the toxic effects of chloromycetin on the erythropoetic organs were exaggerated and should not prohibit its use in suitable cases.

The problem of antagonism or synergism between various antibiotics is discussed in several papers. The opinions were somewhat divergent. Several authors warned against using combinations of penicillin or streptomycin with some of the newer antibiotics such as aureomycin, chloromycetin or terramycin. The combination of sulpha-compounds and penicillin or chloromycetin is considered justifiable in instances of penicillin-resistant cases of viridans septichemia where the newer bacteriostatic antibiotics have shown themselves to be inadequate.

The volume is closed with several articles on the side-effects of antibiotics stressing the superimposed infections caused by resistant bacteria or fungi. Dr. Hedlund reported his experiences with scarlet fever at the Epidemic Hospital in Stockholm showing that there was a decreased immunity after treatment of the disease with antibiotics.

This volume is a good example of the value of the collaboration between clinicians and bacteriologists.

R. Lagererantz, Stockholm.

Emilio Roviralta: **Les vomissements du nourrisson.**

Editions Médicales Flammarion, Paris, 1952. 236 pp. Price 1.800 francs.

In this monograph, Emilio Roviralta, a well known Spanish surgeon, discusses his personal experiences and impressions with a group common disorders in children which produce vomiting. Dr. Roviralta is a children's surgeon at the Institut Policlinique in Barcelona. Because there are no consulting pediatricians at the institute

he has had to make the initial examinations himself and then personally evaluate the diagnostic and practical value of his findings. This gave him a great deal of first-hand experience with these problems. Because he has a curious somewhat sceptical mind, he has not had any difficulty in differentiating between facts and theories. He has always tried to thoroughly explore a problem so that a correct solution may be found. In this book he criticizes pediatricians for their overzealous tendency in labeling vomiting in infants as "habitual vomitings". He demands that every case be given a careful clinical-radiological evaluation to rule out organic diseases. Dr. Roviralta has especially devoted himself to infantile pyloric stenosis and partial ectopia of the stomach. He discusses whether hypertrophic pylorus stenosis is congenital or acquired but neglects to mention that roentgenological evidence of its acquired etiology has been presented by Wallgren and Runström in Sweden. He criticizes the current concept of pylorospasm (i.e. vomitings due to muscular spasm) and maintains that the closure of the pylorus and cardia is a normal finding, and that its relaxation is dependent upon an active function. When one finds such an anomaly of the pyloric lumen there is always another disturbance of some kind that may explain it. Roviralta discusses the hypothesis that during the change from sympaticotonus during the first weeks of life to vagotonus during the following 2—3 months there is a disequilibrium between these two forces. In addition to the neurogenic etiology of this vomiting disorder in young infants he also mentions the influence of a hormonal crisis (folliculin preponderance the first weeks of life, followed by androgen preponderance, until at 4—5 months the estrogen production has started). He also stresses the importance of edema in the mucous membrane of the pylorus canal. The author's concept of treatment corresponds to that of the Scandinavian pediatricians in saying that surgical treatment should be reserved for those cases which do not respond to conservative treatment or those cases in which special care is not readily available. He is very much aware of the fact that many cases of the hypertrophic pylorus stenosis are extremely benign and require only very short period of hospital treatment or none at all.

A special chapter is devoted to the question of the optimal time for operation. Because the course of the disease is so variable his indications for operation are very flexible. He recommends surgical intervention when the infant has lost 1/3 of its body-weight, calculated on the basis of the expected body-weight of a normal infant of the same age.

The author discusses at some length partial ectopia of the stomach with which he has had a vast experience. The incidence of ectopia of the stomach must vary in different parts of the world for it is without doubt much more common in Spain than in Sweden. This difference in frequency cannot be due to a failure to make a proper diagnosis in our country. We have the privilege of having highly trained X-ray men in our clinic who always perform special examinations in cases of vomiting in order to exclude or find disorders in the region of the cardia. Only on very rare occasions have they been able to diagnose this anomaly. He also describes the clinical types, their diagnosis and treatment. A vertical position during the feeding of the infant is recommended.

In other parts of the book he discusses various other disorders which produce vomiting in the infant and newborn period.

The book is of great interest and can be read with great profit.

ANNALES PÆDIATRICI

International Review of Pediatrics · Revue internationale de Pédiatrie

Jahrbuch für Kinderheilkunde

Begründet 1858 von Fr. Mayr, M. Politzer, M. Schuller. Fortgeführt von H. v. Widerhofer, A. Steffen, O. Heubner, Th. Escherich, J. v. Bókay, E. Feer, A. Czerny u. a.

Organ der Schweizerischen Gesellschaft für Pädiatrie — Organe de la Société Suisse de Pédiatrie

2 volumes of 6 parts are published yearly. *Subscription price Sfr. 48.— per volume*
2 volumes de 6 fascicules sont publiés par an *Prix d'abonnement Sfr. 48.— par volume*
Jährlich erscheinen 2 Bände von 6 Heften. *Abonnementspreis Sfr 48.— pro Band*

BASEL (Schweiz) S. KARGER NEW YORK